A Clinician's Guide to Integrative Oncology

What You Should Be Talking About with Cancer Patients and Why

Kylie O'Brien
Avni Sali

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Foreword

O'Brien and Sali have done an outstanding job putting together a book which will be useful to anyone who is interested in integrative medicine. The book provides a new and practical approach to integrative medicine practice. Integrative medicine is a relatively new field of medicine. Most health care providers, patients and even academicians are unaware of the importance of this new way of delivering health care. This requires a new way of thinking about heath and having a holistic approach to the patient. Integrative medicine is patient-centric, individualised preventive patient care focusing on achieving and maintaining health with sustainable every day interventions and developing healthy habits. The physician's role is to make the patient aware of the factors that result in loss of health and give the patient and his/her family the tools to prevent disease.

This book offers practical advice on conducting a comprehensive integrative medicine consultation. Professor Sali's "Ultimate Consultation" and "Ultimate Patient" ideas are right on target and emphasise the importance of spending time to understand the patient as a whole and putting the patient in the driver's seat in making treatment decisions and living a healthy life to prevent chronic diseases. It is very important to empower the patient and give him/her the necessary tools to make decisions and live a healthy and happy life. The book is well organised with chapters on stress, nutrition, sleep, vitamin D and sunshine, exercise, additional therapies and the last chapter brings it all together. Importance of stress reduction, physical activity, healthy diet, sleep as well as nutritional supplements and botanicals are emphasised. Each chapter provides detailed information and a very good summary of the subject area with plenty of references.

The book is easy to read and full of useful information for professionals and lay people alike. I would highly recommend this book to all health care providers as well as to students in the field of health sciences, and the public in general. Healthy living and disease prevention is essential for a happy and productive life.

By implementing the knowledge and strategies in this book, the whole society could become healthier and more productive. This would also reduce health care expenditure and save governments large amounts of money.

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Preface

The idea for this book came about after I sat in on one of Prof. Avni Sali's patient consultations in 2015. The person had cancer, as many of Prof. Sali's patients do. This is not surprising with the 'one in three women and one in two men will be diagnosed with cancer in their lifetime' figures that are regularly splashed around—a rather bleak outlook for the western world to say the least. As a new member of the National Institute of Integrative Medicine (NIIM) consulting in the NIIM Clinic, the largest integrative medicine clinic in Australia, and a Chinese medicine practitioner, I was keen to understand more about Prof. Sali's approach to cancer management. As the '*Founding Father of Integrative Medicine*' in Australia, surely I could learn something from this fellow? And learn I have.

What struck me first is that Prof. Sali's consultations are typically two to three hours long. The patient is listened to and their story is heard. The atmosphere is relaxed but does not detract from the seriousness of what these people face when confronted with a cancer diagnosis. The patient is not told what to do. Their intelligence is respected. They have come for advice on what they can do. In that two- to three-hour period, Prof. Sali walks the patient and, typically, their support person or persons who accompany them, through the steps that they can take to become 'the Ultimate Patient'. The Ultimate Patient is someone who takes an active role in becoming as healthy as they can. In his consultation, which we have termed 'the Ultimate Consultation', the whole person is considered—how stress, diet, lack of exercise and sunlight exposure plus other lifestyle factors can impact on the body in rather complex ways to create illness, and how such factors, when addressed, can assist the patient in achieving a healthier state of being. The focus is on the person, the human being, not just the disease, its pathogenesis and the cancer cells that need to be stopped from replicating.

Integrative Medicine, which combines conventional medicine with evidence-based complementary medicine, therapies and lifestyle interventions for the treatment and prevention of disease, provides the foundation of Prof. Sali's approach. Integrative Medicine empowers patients and health practitioners with a wider range of treatment, screening and prevention options, is actioned via a collaborative relationship and emphasises the promotion of health and well-being.

At this time in history, patients in the western world are voting with their feet—they are choosing to practise their own form of integrative medicine, even if their orthodox medical doctor isn't. A systematic review of complementary and alternative medicine (CAM) use found that prevalence in countries including the United States, Australia, Great Britain, Germany, Italy, Austria, Switzerland, Canada, South Korea, Denmark and others ranges between 5 and 74.5% [4]. Data from the (then-named) National Centre for Complementary and Alternative Medicine in the US (the name has changed to the National Centre for Complementary and Integrative Health) indicated that approximately 38% of adults and 12% of children use some form of CAM [9], whilst in Australia this figure is almost 70% of the population [16].

Studies indicate that people with cancer are high users of CAM. For example, amongst European countries, the prevalence was approximately 36% (range 14.8–73.1%) [6], and data from the 2007 National Health Interview Survey (NHIS) indicate that 65% of those surveyed who had ever been diagnosed with cancer had used 'complementary health' (CAM) approaches [10]. And of course, it is well known that many patients don't tell their medical doctor about their CAM use, for all sorts of reasons. Often, it is simply fear of disapproval. From our experience as clinicians, there are still too many medical practitioners not supporting their patients' choice to do something pro-active and look at a range of options. This behaviour may simply be due to mainstream doctors' lack of knowledge about evidence-based integrative medicine, but it might also have to do with turf wars in some cases too.

Orthodox medicine is, for the most part, dominated by pharmacological and biochemical medicine. This is also true in oncology, with its focus on surgery, chemotherapy and radiation therapy, also known as 'slash, poison and burn'. Whilst there have been some successes with orthodox approaches in effecting a cure from certain cancers, overall the success rate is not spectacular. For example, the benefit of cytotoxic chemotherapy is called into serious question by studies such as one conducted by Morgan and colleagues: a literature search of clinical trials reporting the 5-year survival benefit attributable to chemotherapy alone in adult malignancies found that the overall contribution of curative and adjuvant cytotoxic chemotherapy was 2.1% in the US and 2.3% in Australia [7].

Orthodox western medicine is, in general, inherently reductionist in its approach. That's not to say that such an approach has not been tremendously valuable in many respects. And it's not to say it isn't changing, for example with the various fields of omics like metabolomics opening up. However, the danger is that in focussing on the cancer cells, we miss what we know are the many other factors, including stress, diet, exercise, and the mind, that all impact on the immune system, the gut microbiome, the endocrine system and other systems. Orthodox oncology focuses on the disease, in particular eradicating the cells that are out of control, with chemotherapy, radiation therapy and surgery. Scant attention has been paid in orthodox oncology to the factors that brought the human being into such a state of imbalance that cancer could begin to manifest in the first place. Little attention is paid to treating the whole person, mind and body, nor to helping the patient with

cancer achieve a healthier general state. A healthy person has a better chance of beating cancer than an unhealthy one. The advent of immune-stimulating drugs has caused a level of confusion amongst oncologists because for the first time, there is a need to think about the whole person, and not just the cancer. This is because immunity is about the person. It's not enough to simply remove the cancer, poison it or radiate it.

As far back as 1931 it was recognised by Nobel Prize winner Otto Warburg that cancer cells have a different energy metabolism compared with healthy cells [3]. He found that cancer cells utilised aerobic fermentation, producing lactate in the presence of oxygen, and believed this was due to respiratory insufficiency [3, 11, 12]. Pederson, Seyfried and others found that cancer cells have abnormalities in the content and composition of their mitochondria, and are severely reduced in number in some cancers [3, 11, 12]. The 'Metabolic Theory of Cancer', developed from Warburg's original discoveries, posits that mitochondrial damage is the primary event in cancer, not genetic mutation, which may occur afterwards [3, 11, 12]. This theory, of course, is unlikely to be popular as it challenges the predominant line of thinking in this field, that is, that cancer is essentially caused by genetic mutations. In more recent times, medical oncologist and prostate cancer survivor, Dr. Charles Myers found evidence that prostate cancer utilises LDL cholesterol as a major source of energy, but if LDL cholesterol is lowered, the cancer cell is able to alter its metabolism to use glucose instead as fuel. These findings obviously present some opportunities for the pharmaceutical industry to manipulate metabolism. There are also many other possible ways in which metabolism might be manipulated, without detrimental side effects, for example with diet, stress reduction and exercise.

The gloves have metaphorically come off years ago in the battle to suppress or discredit various forms of CAM. Ralph Moss's book, 'The Cancer Syndrome' [8] details the 'outlawing' of non-conventional medicines including laetrile, vitamin C, and immune therapy. The Bristol Cancer Help Centre (BCHC) was set up decades ago in the UK, at around the same time as the Gawler Foundation in Australia was established by Dr. Ian Gawler. These were the first major centres to establish support systems for patients with cancer, offering CAM therapies, and they were set up outside conventional cancer organisations. A study was conducted to investigate patient outcomes at the BCHC centre in comparison to those at two specialist hospitals and one district general hospital [1], soon after Spiegel's study in San Francisco that showed that an integrative programme of social support with hypnotherapy almost doubled the survival time of patients with metastatic breast cancer in comparison to routine oncological care [14]. The BCHC study was funded by two major UK cancer charities, the Cancer Research Campaign and the Imperial Cancer Research Fund [2, 13]. The BCHC study, published in the prestigious Lancet, found what could only be described as an astounding result that patient outcomes were actually *worse* if they got additional support at the BCHC [1]. However, it transpired that the study was severely flawed in several ways and was widely criticised by medical research experts [15]. For example, some of the criticisms were that the study wasn't randomised and the BCHC included patients who

were much sicker than those who went to the London Hospital at baseline. The researchers eventually admitted that it was much more likely that the differences between the two groups could be explained by the increased severity of disease in the BCHC group [15]. In 1992 a formal complaint against the study was made to the UK Charity Commission by a group of patients who were part of the study, who formed the Bristol Survey Support Group [2, 13]. Some nineteen months later, the UK government's Charity Commission that oversees charities all British charities had completed its investigation and severely reprimanded the two charities that had funded the study for poor supervision [2, 13]. However, by this time much damage had been done to the BCHC and it nearly went into receivership. This underpins the necessity of rigorous research methodology and highlights the damage that can be done when erroneous results reach the press.

Pharmaceuticals equal big money. In contrast, you can't patent complementary medicines easily and you can't bottle meditation. The recent savagery of homoeopathy in Australia is an example of an attempt to discredit the practice, despite its very wide use in European countries, on the basis of, purportedly, a lack of scientific evidence.

For those involved in research, it is well known that it is very difficult to procure government funding for research into other aspects of patient care, because there are often no products to sell that are patentable. Governments have a responsibility to become more informed and fund a broader range of research. Governments also have a responsibility to examine their health funding models. At the level of health systems, doctor reimbursement is biased towards short consultations and selling products (via a prescription pad) rather than selling health.

Despite the dominance of the pharmaceutical industry and various efforts to discredit forms of CAM, governments are starting to recognise the value of Integrative Medicine. For example, the National Center for Complementary and Integrative Health (previously the National Center for Complementary and Alternative Medicine, NCCAM) is part of the National Institutes of Health (NIH) in the United States (US). The US National Cancer Institute's Office of Cancer Complementary and Alternative Medicine (OCCAM) and the Cancer Institute of the Chinese Academy of Chinese Medical Sciences jointly held planning meetings to establish the International Consortium for Chinese Medicine and Cancer in 2014 and 2015, clear recognition of the need to integrate knowledge across medical systems. Orthodox cancer organisations are recognising that cancer sufferers will use different forms of CAM and are providing information on their websites. For example, the American Cancer Society website has a '*Complementary and Alternative Methods and Cancer*' section devoted to information about CAM and provides quite balanced information. The Australian Cancer Council's website provides slightly more conservative information about various alternative therapies. The Clinical Oncology Society of Australia (COSA) is the peak national body representing health professionals from all disciplines who work with cancer patients. COSA has a Position Statement on the use of CAM by cancer patients. This is evidence of some acknowledgement from orthodox structures of a role of CAM in supporting cancer patients.

Education of doctors in Integrative Medicine is becoming more formalised. Integrative Medicine is now a Board-certified clinical speciality of western medicine in the US, indicative of the recognition of its value. It is likely that other western countries will follow suit in the not too distant future. One of Australia's more prestigious universities, the University of Sydney, announced a position of Chair of Integrative Medicine in May 2015.

In western countries like Australia and the US, we tend to look at things from our own western-centric perspectives. However, certain forms of CAM are not 'alternative' in their countries of origin. Chinese medicine is not 'alternative' in China, where Chinese herbal medicine is combined with chemotherapy and radiation therapy treatment of cancer and is also used post-treatment and in palliative care. The concept of cancer is not new to China. In ancient China, the word for 'tumor' was found on 3500-year old oracle bone prescriptions. The *Central Treasury Canon* from the Han Dynasty already recognised that cancer stemmed from endogenous causes and that tumors were a partial consequence of systemic disease [5]. The Chinese medical system differs from the biomedical model in several ways, including importantly an understanding that the various internal organ systems are interdependent, and that ultimately it is a loss of 'balance' internally that leads to ill health. It is inherently holistic in its approach; emotional factors are seen as potential aetiological factors and it does not suffer from the Cartesian split between mind and body. Chinese medicine is but one different medical system. Ayurveda, Tibetan and other traditional medicines all have their own knowledge and models of the human being.

In order to achieve the best outcomes for cancer patients, a more balanced approach is needed: one in which the best of all types of medicines and therapies are considered, and a team approach to assisting the patient is taken. This is an integrated care model. Integrative Medicine is open to all possibilities that the patient may present with. It is not biased toward one particular treatment regime. This is in contrast to conventional oncology which does have a heavy bias towards surgery, radiation therapy, chemotherapy, and other drugs.

This book is not a guide to the various and many orthodox cancer treatments; other books are available for that purpose. This book is a practical guide for clinicians focussed on how to conduct a good integrative medicine consultation, which we have termed 'the Ultimate Consultation'. The Ultimate Consultation starts with the premise that it is the whole person who needs to be considered, not just the disease, and that to achieve the best outcomes (the Ultimate Result), we need the Ultimate Patient. The Integrative Medicine approach, one that takes into account the myriad of factors that have often led to suboptimal health and empowers the patient with a range of strategies that they can employ, provides the foundation for the Ultimate Consultation.

This book is written for medical doctors, in particular oncologists, and CAM and allied health practitioners who have their part to play in assisting patients with cancer, as well as students of these varied health disciplines. It is written for those who wish to provide a more comprehensive consultation that may complement orthodox cancer treatment and importantly empower their patients to be pro-active in their own journey with cancer.

This book is written on the basis of Prof. Avni Sali's practise, as a joint collaboration between the authors. I am indebted to Prof. Sali for sharing his knowledge with us.

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- Chapter 5 **Sunshine and Vitamin D: Dr. Shirley Mcilvenny** MBBCh, MD, FRCGP(UK), FRACGP, DRCOG. Integrative Medicine Practitioner, NIIM Gold Coast (Australia) and CEO of The Food Coach Institute, author of the books—*Stop, Get Ready, GO; Boost Your Brain for Better Business; Eat Fat to Sexy; Herbs, Roots and Shoots to Spice Up Your Sex-Life.*
- Chapter 6 **Integrating Exercise: Dr. Ian Gillam** (BSc (Hons), MSc, PhD, Dip Phys Ed, AEP, ASP, FASMF, ESSAF); Accredited Exercise Physiologist; Sports Scientist (Level 2) and Sports Nutritionist; Fellow, Sports Medicine Australia; Fellow, Exercise and Sports Science Australia; Awarded 'Top 25 Influencers in Exercise and Sports Science in Australia over the Past 25 Years' in December 2016; Member Queensland State Council, Sports Medicine Australia.
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Prof. Avni Sali AM, MBBS, PhD, FRACS, FACS, FACNEM is the Founding Director of the National Institute of Integrative Medicine (NIIM) in Australia. Originally a surgeon, Avni founded the first Graduate School of Integrative Medicine in a University in Australia. In 2009, he established the National Institute of Integrative Medicine (NIIM), the largest integrative medicine clinic, research and education institution in Australia. Often referred to as the 'Father of Integrative Medicine in Australia' and considered a leading expert in integrative oncology, he was recently awarded an Order of Australia for significant service to integrative medicine as an educator, clinician and researcher, and to professional education.

His lifelong work has been the tireless promotion of bringing evidence-based Integrative Medicine into the mainstream medical model to become the medical paradigm of health care.

Chapter 1
The Ultimate Consultation—An Overview

For the Ultimate Consultation you need the Ultimate Patient to obtain the Ultimate Result.
Professor Avni Sali, National Institute of Integrative Medicine, Australia.
We must act on facts and on the most accurate interpretation of them, using the best scientific information. That does not mean that we must sit back until we have 100% evidence about everything. When the state of the health of the people is at stake we should be prepared to take action to diminish those risks even when the scientific knowledge is not conclusive.

Dr. Richard Horton MD, Editor in Chief, The Lancet 1988.

In this chapter we explore:

- What is the Ultimate Consultation?
- Key features of the Ultimate Consultation
- An overview of Seven Key Health Strategies that form the basis of discussion in an integrative oncology consultation

Note on Terminology
In this book, we will use the term 'Integrative Medicine practitioner' to denote a practitioner who is qualified in western medicine and at least one other form of complementary medicine (typically this is often nutritional medicine, acupuncture, an/or mind–body medicine). We will use the term 'complementary medicine' to denote those systems of medicine and therapies that lie outside of conventional (western) medicine, which nonetheless can be complementary to orthodox medical care. It is of course recognised that in defining it as such, we are taking a somewhat Western-centric approach and that in some countries, forms of 'complementary medicine' such as Chinese medicine would not be considered 'complementary'. The term 'complementary medicine practitioner' will be used to denote a healthcare practitioner, whose primary qualification is in a form of complementary medicine and who is not qualified in Western medicine.

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Introduction

Integrative Medicine combines conventional medicine with evidence-based complementary medicines, therapies and lifestyle interventions for the treatment and prevention of disease. The patient–practitioner relationship is collaborative and supportive, empowering patients to take control of their health and well-being. Integrative medical practice makes use of all appropriate therapeutic approaches, healthcare providers and disciplines to achieve the best health outcome for each individual patient. Integrative Medicine empowers patients and health practitioners with a wider range of treatment, screening and prevention options, a collaborative relationship, and an emphasis on preventative medicine. It is a form of medicine through which the clinician can deliver health to the public; in a sense it enables public health.

Integrative medicine requires an integrated care approach, one that respects the various contributions that many therapies and systems of medicine can offer the patient, and respects the right of the patient to make their own decisions regarding their health. The key emphasis of the Integrative Medicine approach is to assist the patient to become as healthy as possible, regardless of the condition they present with. An integrated care model of practice requires the various practitioners involved in the cancer patient care to talk with each other—frequently in some cases!

The more informed the Western medical doctor or oncologist is about various forms of complementary medicine, the better. It is well known that people avoid telling their Western medical practitioner that they are taking complementary medicines or visiting a complementary medicine practitioner. This is likely to be no different in patients with cancer, and it is known that a large proportion of people with cancer use complementary medicines. How much more refreshing and stress-relieving for the cancer patient who would like to try complementary medicines or who is already trying them to be able to discuss this, and even seek advice, from a well-informed oncologist who understands the evidence-base (both scientific and experiential) of various forms of complementary medicine. Even better, the Western medical practitioner who has experienced some complementary therapies is able to offer first-hand experience to the patient. There is also the medico-legal aspect to consider: clinicians should be aware of all of the available options and be able to discuss these with their patients.

In This Chapter

In this chapter, we will explore the features and elements of the Ultimate Consultation so that you, the clinician, may begin to structure your own consultations. In subsequent chapters, we will then explore, in detail, each of these elements which we term ‘Seven Key Health Strategies’ that are discussed with the

patient in a comprehensive consultation. These include stress and stress-reduction in cancer, the role of diet, sleep, sunshine, exercise, supplements and herbal medicines and novel investigative technologies and therapies (Chaps. 2–7). The last chapter sets out how to work within an integrated care model of health care, and how to bring all the information together, in particular by creating a personalised Wellness Plan with your patient that can be used to structure an integrative approach and track their progress.

So, let's first explore what makes a consultation an Ultimate Consultation.

The Ultimate Consultation

Conventional medicine is primarily concerned about making a diagnosis, which then informs the treatment, according to clinical guidelines. A typical medical consultation (though there are of course plenty of individual exceptions) has very little to do with the patient in a holistic sense. There is typically little or no consideration given to the role of stress, diet/nutrition, exercise (lack of) and other important factors that may have led to the patient to a state of disharmony, that has led to the physical disease of cancer. Nor is much or often any attention given to how the patient might change their lifestyle, including these various aforementioned factors, in order to become as healthy as possible. In the end, a healthy patient fares better than an unhealthy patient. In the field of cancer, the conventional oncologists' emphasis is on the cancer: eradicating it from the body through poisoning it or radiating it, and not on the person.

In contrast, the Ultimate Consultation is one which comprehensively considers and addresses the potential causes of 'disharmony', to borrow a term from Chinese medicine. It puts the patient firmly in the driver's seat by empowering them with knowledge and encouraging them to be proactive. It respects their right to make informed choices. In a real sense, the clinician is also assisting the patient to marshal her/his own inner forces and utilise their will and the power of their mind, in order that they have the best chance of overcoming cancer should the patient decide that they do want to overcome cancer.

Consideration of Other Complementary Medicine Modalities

In the Ultimate Consultation consideration is also given by the clinician to other modalities that may benefit the patient. It is well known that patients with cancer, as well as the general population in the US, Australia and other Western countries, are using various forms of complementary medicine, often without their medical practitioner knowing. In an integrative medicine consultation such options should be canvassed with the patient, and the patient's right to explore these options respected. Healing occurs in so many different ways. Do not disparage the patient

for exploring, in particular if you yourself are not firmly across the evidence-base. Instead, be ready with a referral list of trusted integrative medicine and complementary medicine practitioners with whom you may co-manage the patient.

Consideration of Language Used in Discussing Cancer

Whilst it is more common to hear phrases such as 'the war against cancer' or 'battling cancer' or similar, it is worthwhile considering a different approach in the use of language when talking with people living with cancer. Much of the language used in oncology is disease-focused and reductionist, for example 'irradiating the cancer'. Reducing discussion to 'the cancer' misses the very vital human element—the cancer is part of the person, not separate. The idea of 'battling cancer' or waging a war on cancer makes it seem as if it's an outside invader of some kind, when it isn't.

The origins of cancer are still far from precisely understood, however, it is very much part of that person's being. The human body or being has its own intelligence, at the cellular level and going further, at the level of quantum physics where the world of subatomic particles and energy exists. We don't fully understand the human being, the role of consciousness, how the body really works, but perhaps an idea could be that each of us is a gestalt of informed energy and the sum of our experiences. Something has happened to the person who has cancer to have manifested this disease. There is misinformation occurring at a cellular level and underneath this, at an energetic level that has led to the cancer occurring, but still it is very much part of the totality of the person's existence. In Chinese medicine terms, there is a state of 'imbalance' or 'disharmony' within the human being who is ill, and whilst these terms might seem somewhat vague, they are actually quite encompassing as they can be used on a number of levels—physical, mental, emotional and perhaps even spiritual. The point here is to give consideration to how language is and can be used and to remember that the focus is on helping the patient's overall well-being, using language that is reflective of this.

Key Point
Mind your language: the cancer is not something separate from the person to be attacked. It is a reflection of imbalance in the body.

Key Features of the Ultimate Consultation

There are seven key features of the Ultimate Consultation. These are set out in Table 1.1. Let's explore what these are.

Table 1.1 Key features of the Ultimate Consultation

1. For the Ultimate Consultation you need the Ultimate Patient to obtain the Ultimate Result
2. The Ultimate Consultation focuses on **Seven Key Health Strategies**
3. The Ultimate Consultation requires time: typically 1–2 h may be required
4. Information and advice discussed is underpinned by the best available evidence
5. The patient and their support person(s) are empowered
6. The patient takes home something tangible at the end of the consultation.
7. The integrated care model provides the framework

1. ***For the Ultimate Consultation you need the Ultimate Patient to obtain the Ultimate Result***

The Ultimate Consultation starts with the premise that the most important part of the Ultimate Consultation is the Ultimate Patient, one who participates actively in achieving their best health outcomes. This includes enhancing their general, overall health as well as dealing with the specific clinical problems they are facing.

Development of routine is very important and should be emphasised to the patient—this may be developing a routine of exercise, eating healthy foods, getting out in the sunshine, developing good sleep habits, and unloading stress. It is about changing unhealthy habits and replacing them with healthy habits. A healthy patient with cancer will fare better than an unhealthy one. And a patient who participates in getting better will invariably get better results.

Key Point
Development of routine is very important and should be emphasised to the patient.

2. ***The Ultimate Consultation focuses on Seven Key Health Strategies***

The focus of the integrative medicine consultation, in terms of questioning during the case history and information shared by the clinician with the patients, is on **Seven Key Health Strategies**:

- Reducing and unloading the storage of life stresses, and harnessing the power of the mind
- Eating healthy food
- Getting adequate sleep
- Getting a daily dose of sunlight

- Exercising
- Taking supplements and herbal medicines
- Exploring innovative investigative technologies and therapies.

This will involve discussion of stress and its role in cancer, the role of diet in cancer, including foods to eat as well as avoid, the importance of sleep in assisting healing and how sleep becomes disrupted in cancer, the benefit of sunlight and Vitamin D, the role of exercise, useful nutritional supplements and herbal medicines, and innovative investigative technologies and treatments. These seven key health strategies will be discussed in the next six chapters.

3. ***The Ultimate Consultation requires time***

To really listen to the patient's story, and to be able to cover the many issues that need to be spoken about, it is likely the clinician will need to spend much longer than perhaps they are used to spending with patients. This may mean an hour or more of the clinician's time. The time spent at that initial meeting is critical and should not be rushed. It is where and when the clinician can help the cancer patient unburden, assist them to (very importantly) understand elements of their lifestyle that might contribute to illness and how they can change these, and what specific measures they can take with respect to these to achieve better overall health. It is important that the clinician listen to the patient—it is their life, they are paying for your time, and you have taken on a life of service in being a healthcare practitioner. There is a wonderful saying that goes something like this: '*Generally when your lips are moving you are not learning much*'. Let the patient speak. And listen. It is in the being heard and understood that real trust is built between the patient and practitioner, and this is beneficial therapeutically too. There is time enough to put your well-honed knowledge to good use.

4. ***Information and advice discussed is underpinned by the best available evidence***

Clinicians need to be informed about the scientific evidence-base in relation to the many factors that play a role in cancer (stress, diet and others) and the range of orthodox and integrative medicine therapies available to the patient. However, it is also important to realise that complementary medicine systems such as Chinese medicine and ayurvedic medicine, to name just two, have a solid base of experiential evidence derived empirically over thousands of years (as well as quite a lot of scientific evidence nowadays). There is room for both kinds of evidence.

5. ***The patient and their support person(s) are empowered***

Even under the worst circumstances, cancer patients should be made to feel that they have a tomorrow. Oncologists base their prognosis on the limited evidence available based on conventional medicine without being aware of the other available therapies that can help produce a very different prognosis.

One of the greatest gifts that you can give to a patient is a sense of empowerment. Who is anyone to tell someone there is no hope when there are many

examples of people who have overcome various forms of cancer? This is akin to 'pointing the bone' in Australian Aboriginal culture. People are not statistics. They are individuals. Any one individual may overcome their illness, against all apparent odds (statistics again). The mind is the most powerful aspect of the human and its potential in healing is largely ignored by conventional medicine. In the Ultimate Consultation, the clinician helps empower the patient with cancer to take control of those many factors that they can control (stress, diet, exercise, sunlight, adequate sleep and others). Improving these factors can assist the patient to enhance their immune system and bring themselves back into balance.

Key Point
The consultation should empower the patient through knowledge of how they can create positive change within themselves.

6. ***The patient takes home something tangible at the end of the consultation***

At the end of the consultation, the patient takes home a printed patient summary of information about the ***Seven Key Health Strategies*** discussed during the consultation. In addition, the patient may take home a copy of her/his personalised Wellness Plan that she/he has worked through with their clinician during the consultation, or a blank one which they may choose to work on themselves, for discussion at the next consultation. This can be used by the patient and their clinician to record scheduled appointments for various therapies, chart their progress, or simply record the patient's thoughts. This is discussed further in Chap. 8.

7. ***The integrated care model provides the framework***

The Ultimate Consultation sits within an overarching framework of care for the patient with cancer that is the 'integrated care model'. What individual people understand by 'health' is complex, not necessarily uniform across populations, and multi-dimensional. As defined by the World Health Organisation in 2001, '*health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*' [1]. There are many forms of complementary medicine that people with cancer may like to explore as part of an integrated approach to managing their disease and its symptoms, signs and impact on self. In an integrated care model, Western medical doctors work with other healthcare providers, including complementary medicine doctors and therapists, psychologists, massage therapists, and spiritualists and the patient, to provide an integrative approach to their care.

Conclusion

The Ultimate Consultation is one in which an integrative medicine approach is taken to assisting the patient with cancer to improve their general well-being as well as deal with specific concerns. It is based on the premises that a healthy person with cancer has a better chance than an unhealthy person with cancer and that a person who is actively engaged in improving their health is likely to achieve better results. The Ultimate Consultation recognises the benefits of all forms of useful medicine. It does not position orthodox medicine above other forms of medicine; rather it considers all forms of therapies and treatments and empowers the patient, through evidence-based knowledge, to make their own choices about how they manage their illness. Importantly, it places value on an integrated care model, one in which a team of dedicated healthcare practitioners work together with the patient, to help provide the best strategies.

Summary: Seven Key Health Strategies

- Reducing and unloading the storage of life stresses, and harnessing the power of the mind
- Eating healthy food
- Getting adequate sleep
- Getting a daily dose of sunlight
- Exercising
- Taking supplements and herbal medicines
- Exploring innovative investigative technologies and therapies.

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Chapter 2
Let's Talk About Stress

Mind-body medicine- this is the main area where miracles can occur.

Avni Sali

In this chapter we explore:

- Why stress is important including the associations between stress, depression, anxiety and cancer, and the relationships between stress and depression and the endocrine system, immune system and the gut microbiome
- What happens at the cellular level when there is stress, including how it affects the immune system, endocrine system and gut microbiome
- What to do about stress in the Ultimate Consultation including beginning the conversation about stress and techniques for unloading stress and stored emotions.

Introduction

How a person feels is paramount to their health and whether they look after themselves. If a person feels good, they tend to care more for themselves, however when they do not feel good about themselves, they often do things that are counterproductive to good health. This includes not exercising, eating the wrong foods, smoking and drinking excess alcohol. The way the mind influences the body is perhaps the most important area in medicine. Known as mind-body medicine, there is now much science that helps us understand the way we are able to influence our physical selves, by how we behave and what we do.

Hans Seyle (a pioneering Austrian-Canadian endocrinologist) was the one of the first people to recognise the role of stress in the human body, though not the first to use the word [114]. Seyle in 1936 defined stress as 'the non-specific response of the body to any demand for change' [114]. He was the first to recognise the role of hypophysis-adrenal cortex axis in the stress response [114].

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Stress and pleasure play a crucial role in wellness and disease [118]. Stress describes the effects of psychological and environmental factors on the human's well-being, on a number of levels including physical, emotional and mental. However, even if a person is stressed, if they are feeling good then stress is likely to have fewer negative effects [118]. Stress is also less likely to cause health problems if there is an emotional outlet for it [118].

In This Chapter

In the first part of this chapter, we will explore why stress is important and how it impacts on health and the functioning of the mind and body. In the second part of this chapter, we will look at what can be done about stress in the Ultimate Consultation.

Why Is Stress an Important Factor in Our Health?

Stress affects every system in our body including the immune system, endocrine system and the gut. All these play important roles in physiological homeostasis, and disturbance of functioning is implicated in a range of diseases including cancer. The ancient Chinese knew very clearly that emotions were an aetiological factor in the pathogenesis of disease. Certainly, it is the clinical experience of Professor Sali's that the greater the stress and the worse the personal circumstances are, the greater the likelihood of a cancer with poorer prognosis. A study of breast cancer patients has confirmed this clinical experience [97]. From our Western scientific literature, we see the evidence of a relationship between mind, emotions and the functioning of the body at the level of cells and tissues, as well as at the epidemiological level when we look at patterns of associations between mental illnesses such as depression and cancer. Let's look at some of the evidence.

Storage of Emotions and Its Relationship to Illness

The storage of emotions, at the level of the subconscious mind but also in a more tangible sense, within the physical body, and its relationship to illness is one of the most important concepts that the clinician will need to impart to her/his patient. It is the experience of the authors that many, if not most cancer patients, tend to be sensitive types—that is, they are the ones who pick up and absorb the stress around them. Of course, most people in the Westernised world are exposed to plenty of stresses. However, for some, this is simply 'water off a duck's back', as the saying goes. Those people tend to fare better healthwise. The sensitive person is more

likely to pick up external factors and stressors, storing them internally and adversely affecting immunity and hormones. This can lead to excess worry, anxiety, stress, sleeplessness and other problems. If the sensitive person keeps all these emotions inside rather than 'unloading', for example, sharing with a close confidant, then they are at greater risk of illness. Here are some of the reasons why stress is an important factor in our health.

Associations Between Stress, Depression, Anxiety and Cancer

There is evidence that stress is implicated in cancer initiation and progression at an epidemiological level. Although the literature is somewhat divided on whether major life events are associated with increased risk of cancer, some studies indicate that stressful life events can precede cancer [28, 63] and that stress-related psychosocial factors are associated with higher cancer incidence and poorer survival [19]. It is certainly our experience that in many cases, there has either been a history of ongoing stress or in many cases, a traumatic event preceding a diagnosis of cancer.

There is also some evidence of a relationship between coping styles and emotional responses and cancer incidence and survival [19]. For example, a depressive coping style and emotional distress have been found to be associated with poor survival in lung cancer patients [30].

Table 2.1 sets out some evidence from observational studies about the link between stress and cancer.

There is also a link between psychological distress such as anxiety and depression, and cancer. Depression is common in cancer patients, affecting up to 25% [46, 64]. There is evidence to indicate that depression may be associated with an increased risk of cancer and may predict cancer progression [92, 108]: the longer

Table 2.1 Stress and cancer: evidence from some observational studies

• A review of 165 studies found that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations, poorer survival in patients diagnosed with cancer (330 studies), and higher cancer mortality (53 studies) [19]
• Stress-prone personality, unfavourable coping styles, and negative emotional response were related to higher cancer incidence, poorer cancer survival and higher cancer mortality [19]
• The Finnish Twin Cohort study found an association between the accumulation of life events during 5 years prior to baseline assessment and increased risk of breast cancer: divorce, separation, death of a husband/close relative/friend were all associated with increased risk of breast cancer [63]
• Prior stressful experiences in childhood have been linked to decreased cellular immunity and depressive symptoms in breast cancer survivors [28]

the duration of depression, the greater the risk of developing cancer [85]. Risk of developing cancer due to depression is almost doubled, independent of other lifestyle factors, and this risk is not related to any specific cancer [92]. Depressive symptomatology has been found to be a consistent psychological predictor of decreased survival time [17].

Coexistence of Anxiety and Depression in Cancer

Anxiety and depression often coexist in cancer patients. In a large epidemiological study of women diagnosed with breast cancer, 10.8% had combined anxiety/depression symptoms (CADS), 14.9% had only anxiety symptoms and 2.8% had only depressive symptoms [16]. Another study found that 44.5% of women with breast cancer were diagnosed with CADS, and that higher levels of anxiety with or without sub-syndromal depressive symptoms were associated with higher fears of recurrence and decreased life satisfaction [40]. In addition, both anxiety and depression have also been found to be associated with cancer-related fatigue, a symptom that affects a significant percentage of cancer sufferers [47]. And as Kotsirilos and colleagues point out [56], depression can also influence lifestyle factors that may negatively impact on health including smoking, consuming an excess of alcohol, poor level of physical activity and excess weight [45].

Table 2.2 sets out some of the facts and figures about the relationship between anxiety, depression and cancer.

Table 2.2 Some facts and figures about anxiety, depression and cancer

• Depression affects 15–25% of cancer patients [46, 64], with a higher prevalence in female cancer patients compared with male [22]
• Studies indicate that anxiety and depression can coexist in 10–45% of breast cancer patients [16, 40]
• Chronic and severe depression may be associated with elevated cancer risk and there is evidence that depression predicts more rapid progression of cancer [108]. The longer that depression has existed, the greater risk there is of getting cancer [85]
• Depression [95], stressful life events [19, 43] and social isolation [96] have been found in meta-analyses to be linked with poorer survival in cancer patients.
• Depression prevalence in cancer patients has been found to increase with disease severity and symptoms such as pain and fatigue [108]
• There is some evidence that depression predicts cancer progression and mortality (though this is complicated by several factors including that some cancer symptoms and cancer treatment can mimic depression, and disease progression can have a negative effect on mood) [108]
• Perceived stress, anxiety and pain severity have been found to be significantly associated with greater severity of cancer-related fatigue [47]
• Anxiety and depression has been found to be significantly associated with cancer-related fatigue [86], one of the most prevalent symptoms that cancer patients experience during and after treatment and in disease-free survivors [8]

Key Components of Cancer Pathogenesis

Before we take a look at how the mechanisms of how stress may create changes at the cellular level that may contribute to cancer, we will look briefly at the key components of the microenvironment associated with cancer, or the 'hallmarks of cancer'. These are the (so far) known pathogenic events that are present in cancer. These include: sustaining proliferative signalling, evasion of growth suppressing signals, resistance to apoptosis (programmed cell death), replicative immortality, ability to induce angiogenesis, ability to invade and metastasise, ability to evade destruction by the immune system and a reprogramming of energy metabolism, underpinned by genome instability and inflammation [44].

Inflammation is a key aspect of the biochemical environment associated with tumors, as it is with other chronic diseases including diabetes and other cardiovascular diseases. Lung, colorectal and breast cancer have all been found to be associated with high levels of C-reactive protein, an inflammatory marker and a stronger association has been found between increased levels of inflammatory markers and risk of cancer death compared with the risk of cancer incidence [49].

Sex hormones have also been implicated in the pathogenesis of some cancers such as breast and prostate cancer, though for prostate cancer, there is mixed evidence for the role of testosterone in carcinogenesis [75].

Insulin and IGF, and oxidative stress are also involved. In cancer, oxidative stress and the production of free radicals occur at a much higher rate in cancer cells than normal cells [9]. Increased insulin can stimulate tumor development and progression, including cancer cell proliferation and migration in cancer cell lines [26] and has been found to have mitogenic and anti-apoptotic effects in endometrial cancer [119]. Oxidative stress can increase mutagenesis and DNA mutation rate and upregulate angiogenesis, disrupt mitochondrial functioning (causing fatigue) and accelerate tumor sculpting [9].

What is happening at the cellular level is obviously very complex. The reader is referred to other sources for detail on the cancer pathogenesis.

The Cellular Level: Stress, Endocrine and Immune Systems and Cancer

Stress and depression influence the body through the brain: psychoneuroimmunology (PNI) is the study of how the mind influences the immune system (to be normal, abnormal or hyperactive), and psychoneuroendocrinology (PNE) describes how the mind influences the body's endocrine system [103]. Inflammation, a key process in cancer and other chronic diseases, is modulated via bidirectional communication between the neuroendocrine system, immune system and the brain [118], with increasing evidence of the role of the gut microbiome (more later).

Stress is able to activate the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis and thereby alter the tumor microenvironment. When stress activates the HPA axis, corticotrophin-releasing hormone (main regulator of HPA axis) is secreted and this induces the release of adrenocorticotrophic hormone into the systemic circulation, where it stimulates the adrenal cortex to produce glucocorticoids. Glucocorticoids (e.g. cortisol) along with catecholamines (noradrenaline and adrenaline) from activation of the autonomic nervous system are released into the bloodstream as part of the stress response, as are inflammatory cytokines [23, 68]. These can all affect the tumor microenvironment. Glucocorticoids can also directly mediate processes that promote tumor growth, activate survival genes in cancer cells, down-regulate repair genes and inhibit the cellular immune response [68]. Stress has also been shown to influence many parts of the steps involved in metastatic spread of cancer [68].

Stress and the Immune System

Chronic stress, via activation of the HPA axis, results in the release of various mediators that can suppress some of the non-specific and specific parts of the immune response including NK-cell activity, phagocytosis, production of inflammatory cytokines (e.g. IL-2, interferon, TNF by Th1 cells) and activity of cytotoxic T cells, all of which are important components of the cancer surveillance and the immune response against cancer [68, 99]. Psychological stress also reduces the ability of cells to initiate genetically programmed cancer cell death [116].

Chemical messengers secreted by nerve cells, endocrine organs or immune cells mediate the communication between the central nervous system (CNS) and the immune system, and psychological stress can down-regulate various parts of the cellular immune response, disrupting these communication networks between the CNS and immune system [99]. Bio-behavioural oncology research has found that stress can not only down-regulate the cellular immune response (mediated largely by adrenergic and glucocorticoid signalling) but that it can also affect tumor angiogenesis, invasion and anoikis, stromal cells in the tumor microenvironment and inflammation, all pathways involved in cancer [68].

Interventions that reduce psychological distress have been found to create changes at the cellular level, for example, significantly increasing the percentage of large granular lymphocytes and increasing NK cytotoxic activity in patients with malignant melanoma [31].

Stress and Chronic Inflammation

There is strong evidence that chronic inflammation precedes tumorigenesis [59] and that the stress response and inflammation play an important role in the pathogenesis

of cancer metastasis [68, 91]. Chronic stress can lead to inflammation through the production of cytokines, including interleukins [68, 99]. People with major depression have been found to have increased production of pro-inflammatory cytokines interleukin 1, interleukin 6, soluble interleukin 2 and interleukin 6 receptors, suggesting that concentrations of pro-inflammatory cytokines correlate with HPA activity and disease severity [99]. Stress increases the level of cytokines such as Vascular Endothelial Growth Factor (VEGF), a cytokine which mediates angiogenesis and cancer patients with high levels of VEGF have a poorer prognosis [45]. Cytokines can also stimulate tumor growth [45].

Stress and the Endocrine System

Stress and depression can alter the functioning of the endocrine system, leading to increased insulin secretion from the pancreas, increased cortisol, growth hormone and prolactin, which can contribute to increased tumor growth [56]. Neuroendocrine stress hormones, released via the brain, sympathetic nervous system and/or HPA axis, in the tumor microenvironment assert a systemic influence on tumor growth [68]. High cortisol levels (and a tendency towards flatter diurnal cortisol rhythms) have been found to be associated with greater disease severity in women with metastatic breast cancer [1]. Other research in women with early metastatic breast cancer found that women who repressed emotions and those who were highly anxious had a significantly flatter diurnal cortisol slope than self-assured and non-extreme groups, though there was no difference in mean cortisol levels [36].

In patients with depression, cortisol was found to be increased in those who were chronically stressed, suggesting that depression is associated with sensitisation of the HPA axis to chronic stress [110]. As previously stated, depression affects a significant proportion of cancer patients [22, 46 and 64].

Corticotropin-releasing factor (CRF) is a hypothalamic neuropeptide that is involved in the control of the stress response. It is also expressed in organs and peripheral tissues [6]. In the tumor microenvironment, it may be produced by innervating sympathetic neurons, immune cells and endothelial cells [5, 6]. CRF has been found in breast cancer cells and tissue and can affect breast cancer cells in an autocrine or paracrine manner [5]. Research has found that CRF stimulates cell motility and invasiveness of breast cancer cells, and that the likely mechanism is via induction of Focal Adhesion Kinase (FAK) phosphorylation and the reorganisation of actin filaments and the production of prostaglandins: CRF induces the production of prostaglandins and expression of Cox-1 in breast cancer cells, which are factors that can promote invasiveness and metastasis [5]. In vitro, research has found that CRF can induce the expression of genes involved in breast cancer proliferation and metastases. In vivo, research has also demonstrated that peripheral CRF at least partly mediates the tumor-promoting effects of stress (including neoangiogenesis and tumor growth) [6].

Stress and Genetic Damage

Stress can lead to DNA damage, accumulation of somatic mutations, impaired genetic mutation repair and inhibition of apoptosis [39, 50, 99]. In human studies, perceived psychological stress and perception of inability to alleviate stress have both been found to be associated with increased levels of 8-hydroxydeoxyguanosine (8-OH-dG), a biomarker of cancer-related oxidative DNA damage, in females but interestingly not in males [50]. In healthy workers, the levels of 8-OH-dG were higher in females with poor stress-coping behaviours and in males with a self-blame coping strategy [51].

At the Cellular Level: Stress, Depression, Anxiety and the Gut

The gut microbiome is assuming a much greater importance than previously given credit for in the stress response. The interaction between stress, the HPA axis and immune system is well established, and it is now believed that the gut microbiota mediates this response [23].

The newborn child is exposed to the maternal vaginal microbiota during childbirth, providing the main source for normal gut colonisation, host immune maturation and metabolism [52]. Microorganisms within the gut form part of a complex and multidirectional communication network with the brain, the microbiome-gut-brain axis [106]. The gut contains as many neurons as the spinal cord and there are many hormonal connections [42]. The microbiota and host, the human, have co-evolved into a complex 'super-organism' which has been beneficial to the host, but it can also create problems when the microbiota becomes dysregulated or disturbed. Each organ has a microbiome; however, 99% of the microbial mass is in the gastrointestinal tract [105].

The Gut and the Immune System

The gut microbiome is now understood to play a critical role in the functioning of the immune system, thereby influencing inflammation, as well as the nervous system [93]. The gut microbiome plays a key role in regulating intestinal permeability and maintaining the intestinal barrier function and deficits in intestinal permeability may be a causal factor in the chronic low-grade inflammation observed in depression [54]. A U.S. study found that major depression is accompanied by activation of the inflammatory response system and that pro-inflammatory cytokines and lipopolysaccharide (LPS) may induce depressive symptoms—a significant increase in level of antibodies against LPS in the blood was found in those with

major depression [71]. LPS, the major component of the outer membrane of certain bacteria, is able to enter the bloodstream only if the normally tight junctions in the cells lining the intestine are compromised and the intestine lining becomes permeable or 'leaky' [93]. It can then fuel inflammation. Inflammation is a key component of many chronic diseases including cancer.

Regulation of Moods by the Microbiome-Gut-Brain Axis

The gut microbiome has been found to affect neural, immunological and endocrine systems, with the microbiome-gut-brain axis modulating emotions and moods. Stress is able to modulate the microbiota and the microbiota is able to alter the set point for stress sensitivity [106]. The gut microbiota generates several neurotransmitters including gamma-aminobutyric acid (GABA), acetylcholine, dopamine, norepinephrine and serotonin [42]. Neurotransmitter imbalances or deficiencies are known to cause psychiatric problems such as depression [42]; altered GABA receptor expression is implicated in the pathogenesis of anxiety and depression (both of which are associated with functional bowel problems) [15]. Depression has been found to be associated with dysregulation of the gut microbiota composition [106].

Animal research demonstrates clear links between the gut microbiome and stress/anxiety/depression as well as changes in the brain. This includes findings that

Table 2.3 Pre-clinical (animal research): gut microbiome, stress, anxiety and depression

• Germ-free mice have an exaggerated HPA axis response to restraint stress which was reversed by moncolonisation with Bifidobacterium infantis [113]
• Female mice stressed during pregnancy pass on lowered levels of gut bacterium to their pups [52]
• Increased stress was found to be associated with decreased microbial diversity in the gut of wild red squirrels [111]
• Absence of the gut microbiota in rats exacerbated behavioural responses to acute stress and was associated with an altered neurotransmitter turnover rate in areas of the brain known to regulate reactivity to stress and anxiety-like behaviour [20]
• Short-term colonization of germ-free adult mice was found to reduce anxiety-like behaviours [84]
• Research has demonstrated that normal gut microbiota is critical for normal social development in mice [24]. Treatment of mice with probiotics can reduce early life stress-induced immune changes [25], depressive-related behaviours [15, 25] and anxiety-like behaviours [69, 87]
• Lack of normal gut microbiota in mice is associated with decreased expression of BDNF in the hippocampus, a key protein involved in neuronal plasticity and cognition [72, 73]
• Treatment of mice with Lactobacillus rhamnosus (JB-1)-induced changes in GABA mRNA expression in areas of the brain and reduced stress-related cortiocosterone and anxiety and depression-related behaviour, with the Vagus Nerve implicated as the major modulatory pathway between the gut and the brain [15]
• Germ-free adult mice exposed to faecal microbiota from pathogen-free donors had decreased blood-brain barrier permeability and increased expression of tight junction proteins [14]

the gut microbiota can modulate the blood-brain barrier [54]. How translatable such findings are to humans in understanding brain-gut relationships and disorders is not yet known [72, 73]. Some key findings from pre-clinical (animal) research are set out in Table 2.3.

The relationship between the gut microbiome and emotions and stress is an important and complex one. However, there is increasing evidence that the gut microbiome and brain, immune and endocrine systems are all in constant communication, and the gut microbiome is a key player in the stress response. And the storage of emotions and stress is closely linked to the pathogenesis of cancer.

The Gut Microbiome and Cancer

There is increasing evidence that the bacterial microbiota plays a key role in carcinogenesis [105]. Whilst particular cancers are triggered by specific bacteria (e.g. gastric cancer and *Helicobacter pylori*), other cancers such as colorectal cancer appear to be triggered by tumor-promoting effects of microbiota (e.g. liver cancer may be promoted by pro-inflammatory micro-organism associated metabolic patterns (MAMPs) and bacterial metabolites from the intestine, via the portal vein) [105]. Colorectal cancer (CRC) has been found to be associated with decreased overall microbial community diversity and relative depletion of the Clostridia class of Firmicutes bacteria. Increased risk of CRC was found with increased carriage of Atopobium, Fusobacterium and Porphyromonas bacteria [3].

Use of antibiotics, known to disturb the gut microbiome, has been shown to be linked to an increased risk of breast cancer and of fatal breast cancer: a U.S. study demonstrated that there was a significant correlation between antibiotic use and terminal breast cancer [117].

Disturbances in Anatomical Barriers

Disturbances of the anatomical barriers between the host and microbes can also promote inflammation and diseases including cancer. The relationship is bidirectional: barrier failure can trigger inflammation, and inflammation and carcinogenesis can promote barrier failure [105]. These are but a few of the potential pathways of involvement of the microbiota; the mechanisms involved in carcinogenesis are complex. The reader is referred to other sources for a more complete explanation.

Obesity and Microbiotal Dysbiosis

Obesity, a major modifiable risk factor for the development of many types of cancer, is associated with microbiotal dysbiosis which may result in several

physiological changes that could contribute to the link between obesity and cancer. These include altered microbial metabolism that can contribute to the generation of pro-carcinogenic toxic metabolites, induction of subclinical inflammation that could initiate tumor formation, and/or increased extraction of energy and nutrient availability causing metabolic dysregulation, thereby contributing to tumor growth [101].

The Gut Microbiome During Chemotherapy

The gut microbiome, of course, undergoes quite a beating during chemotherapy, with a severe compositional and functional imbalance in the gut microbiome associated with chemotherapy-induced mucositis [77]. Research has established that over the course of chemotherapy, there is a significant decrease in oral and intestinal microbial diversity and an increase in specific microorganisms known to cause infection [4]. A patient's microbial diversity, even *prior to cancer treatment*, can be linked to increased risk of infection during induction chemotherapy. Thus researchers have suggested that microbiome sampling could be used to predict the chance of infections during chemotherapy, and that monitoring a patient's microbiome during induction chemotherapy could be used to predict risk of microbial-related illness during subsequent treatments [4]. A depleted gut microbiome following chemotherapy leaves the patient with a greater risk of future illness.

Suffice to say, the gut microbiome is an important player in the pathogenesis of cancer. Given its role in influencing the immune, nervous and endocrine systems, including its role in depression which often coexists in cancer sufferers, addressing any imbalance in the gut will be important.

Social Support and Cancer

There is evidence of the impact of lack of social support in those with cancer. Tumors from high risk ovarian cancer patients (high levels of depression and low levels of social support) were compared with tumors from low risk patients (low levels of depression, high levels of social support)—it was found that tumors from high risk individuals showed more than 200 upregulated gene transcripts, many of which were involved in tumor progression. In addition, high risk patients had increased intra-tumor norepinephrine [67]. The association between storage of emotions and cancer is demonstrated in the findings of a systematic review that found that depression and constraint of emotions were associated with decreased survival in breast cancer patients [29].

Loneliness has been found to be related to higher levels of tumor vascular endothelial growth factor (VEGF) in patients with colon cancer [82]. In breast cancer patients, women with low levels of emotional expression and perceived

emotional support were found to have poorer survival than women reporting high levels of both, and use of emotion-focused coping strategies was significantly associated with better survival [100]. A study of 9247 women with breast cancer found that women who were socially isolated women (small networks) were 1.43 times more likely to have a breast cancer recurrence, 1.64 times more likely to die from breast cancer and 1.69 more likely to die of any cause than socially integrated women [57]. Another study of people with cancer found that being unmarried carried a 27% and 19% higher risk of death in men and women, respectively, compared with their married counterparts [41].

Good News

The good news is that research indicates that social support can positively influence cancer survival, discussed in the later sections of this chapter.

What to Do About Stress in the Ultimate Consultation

In the Ultimate Consultation, the clinician's role is to help the patient with cancer understand the link between the mind, stress and those processes in the body that contribute to poor health, and to harness the power of their mind to positively impact their health. The clinician can then guide the patient to several techniques that can help alleviate stress and in particular, unload the storage of stress and emotions.

The clinician will need to allow plenty of time for the consultation, in the order of 1–2 h. The benefit of taking this time will be tremendous, for both patient and clinician. Patients invariably are very appreciative of the opportunity to talk, in detail, with their clinician, and in many ways, this is part of the unloading of stored stresses and emotions itself. Importantly, this is an opportunity for both patient and clinician to understand what factors may have led to the patient becoming out of balance, and for the clinician to empower the patient to be proactive in not only changing those factors that can be changed, but also adopting other strategies to improve their well-being. Remember, the Ultimate Result (whatever that is for the patient, but ideally at the very least an improvement in health and well-being) really depends on the Ultimate Patient, one who is empowered and pro-active. The Ultimate Consultation is fundamentally about enabling and facilitating that empowerment.

Key Point
Allow plenty of time for the consultation, in the order of 1–2 h.

Beginning the Conversation About Stress

Mind Your Language

The language the clinician uses is most important. At the very outset, it is important to remember this is a person *with* cancer you are talking to, and the cancer is part of them, it originated due to imbalance within them, and it is a reflection of what is happening within them as a person. The cancer is *not* a separate, external entity and therefore 'it' cannot be 'aggressive' (as compared with an external infectious organism which could be described as aggressive). In the world of oncology, cancer is treated almost like a separate, external entity to be removed, poisoned or irradiated. This type of thinking may have evolved from the world of infectious diseases where microbes were the infectious agent, the enemy to be gotten rid of. The language that has evolved around this still positions cancer as something separate and unfortunately, the focus of many oncologists is on the disease, the tumor, the cells and not the human being.

Opening up the Conversation About the Patient's Life Stresses

To open up the conversation about stresses in the patient's life, Professor Sali typically begins with handing the patient a diagram such as the one in Fig. 2.1 that sets out in diagram form the relationship between the mind/stress/depression and the immune system, the endocrine system and the gut microbiome. He explains the different components involved in the stress response, including the link between the mind and storage of emotions and stress and the link between the mind/depression/nervous system and the immune system, endocrine system and the gut. Professor Sali elaborates on the concept of storage of emotions and stress, and how one can, by relieving some of the stresses in one's life, positively influence health (via those afore-mentioned interdependent systems).

Talking through this diagram can be an ice-breaker—a means of opening up a discussion with the patient about *their* life stresses. It is most important that patients with cancer understand how stress negatively impacts on them, and come to identify what stresses might be present in their own lives. If the patient can understand what stresses may have contributed to their deviation from wellness, they may be in a better position to make the necessary changes to alleviate their stresses that will then contribute to positive changes in terms of the various bodily systems involved. As there is some evidence of traumatic events preceding a diagnosis of cancer, it is worthwhile talking with the patient about whether there have been any major events such as a death of a loved one.

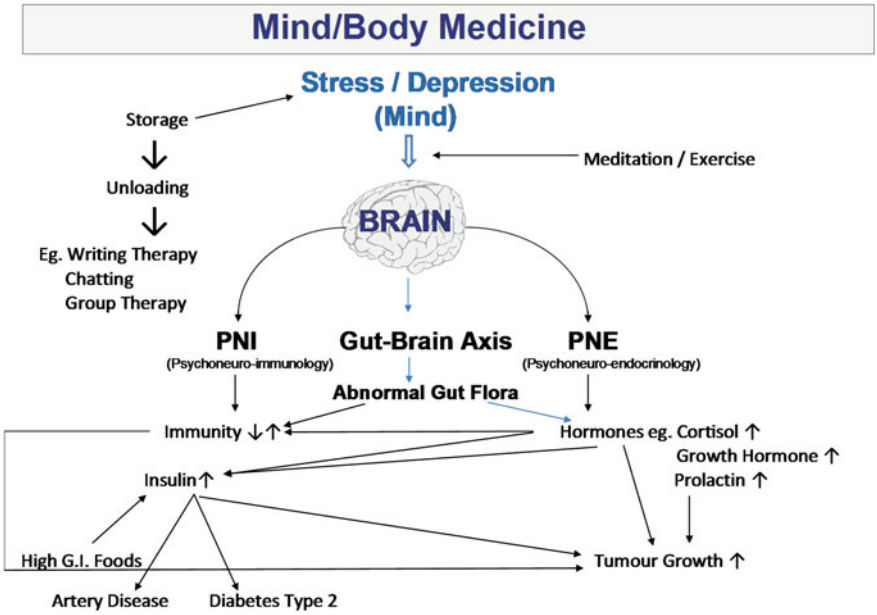

Fig. 2.1 Mind/body medicine

Listening to the Patient's Story

At this point, the clinician needs to sit back and listen, and simply prompt the patient to consider and talk about what difficulties they might be facing. This part of the consultation is critical, and in many ways facilitates a feeling, by the patient, of being heard and understood. Therefore, do not rush this part of the consultation—there is plenty of time for you to impart your knowledge. Listen carefully and you will be able to pick up important clues.

In discussing the link between mind/emotions and the body, it is important that the patient is not left feeling in some way guilty or anxious that they have somehow brought the cancer on themselves or 'drawn' cancer to them, for example, through negative thinking or actions. This is simply neither the case nor helpful to the patient. The power of the mind to positively impact on various pathophysiological pathways should be emphasised, as should how they can be proactive in changing the status quo—this is about empowering positive change through the power of the mind.

The discussion on storage of stress and emotions then leads onto a discussion on how the patient can help themselves by decreasing the storage of stress and emotions: by 'unloading storage'.

Probing About Social Support

Unloading of stress and emotions is important in the prevention of illness, including cancer, and as part of a therapeutic approach. Social support and its role in unloading are extremely important. The disadvantages of poor social support have been discussed in the previous section. Therefore, the clinician should probe whether the cancer patient has social avenues for unloading in their personal life. If not, then there are professional options including working with a psychologist, cancer support groups, and other therapists. And there are other ways to unload stress and emotions, discussed later in this chapter.

Things to Look Out for

The conversation about stress is not a one-off conversation. It should be an ongoing dialogue over subsequent conversations, and an opportunity to check in with how the patient is doing.

Some things to look out for in consultations include symptoms and signs of:

- Anxiety
- Depression
- Cancer-Related Fatigue.

During the initial and subsequent consultations, the clinician will need to be sensitive to the level of anxiety that the patient is likely to be experiencing, particularly on initial diagnosis but also at other time points. For example, following surgery, chemotherapy or radiation therapy, a patient will likely be extremely anxious about follow-up pathology results. Where results are not positive, or where the symptoms and signs associated with the cancer or cancer treatment are impacting physically on the patient, anxiety and depression can compound an already extremely difficult experience.

As we learned earlier, depression can also influence lifestyle factors that may negatively impact on health including smoking, consuming an excess of alcohol, lack of physical activity and excess weight [45]. So it is good to question the patient about their smoking status/habits, alcohol consumption and other lifestyle factors and gently probe to see if they are leaning on any of these as a crutch; lack of or a decrease in physical activity and increase in weight gain in someone who has previously indicated they were active may give some clues as to their current state of mind.

Assist the Patient to Explore Treatment Options for Anxiety and Depression

An integrative medicine approach will encourage the patient to explore various treatment options to help them with their anxiety and depression. For example, a timely referral to a psychologist or counsellor or a cancer support group may assist the patient work through and cope with anxiety and/or depression. At the very least, how the experience of cancer is impacting on the patient emotionally should be discussed with the patient at each consultation. The emotional aspects of what the patient with cancer and their loved ones are facing are critical to address, as the patient has much to gain if they can use their mind positively to impact their health. There is enough research to demonstrate how anxiety and depression can negatively impact on the body, creating in some ways a negative spiral.

Key Points

- Be vigilant at all consultations for symptoms and signs of anxiety, depression and cancer-related fatigue
- Refer the patient to an appropriate professional or support group for help to address the anxiety and depression.

Talking of Happiness

As humans, we have many things in common. One is that most humans seek happiness. It is an important goal to pursue. The fourteenth Dalai Lama says:

> Whether one believes in religion or not, whether one believes in this religion or that religion, the very purpose of our life is happiness, the very motion of our life is toward happiness (His Holiness the Dalai Lama and Cutler [21]).

In healing from cancer and other serious diseases, it is useful to help the patient tap into what brings them happiness. Some people are so caught up in their anxiety, stress and emotional pain that they have lost sight of what brings them joy. If the patient can engage in activities and with people that bring them a sense of happiness, this can have enormous emotional, spiritual and physical healing benefits. When someone is truly happy, stress very often just wilts into the background. In the end, it is our response to external stresses or internally created ones, that determines whether an event is stressful or not.

Techniques for Unloading Stored Stress

There are several techniques that the clinician may suggest to the patient to assist with unloading of stored stress and emotions. Development of a routine is extremely important and should be emphasised, whatever activities they decide to try. Techniques for unloading include the following:

- Stress management through social therapy
- Pet therapy
- Art therapy
- Writing therapy
- Color therapy
- Gardening
- Meditation
- Spirituality and religion
- Multimodality programmes
- Tai chi and qi gong
- Others, including exercise.

It is crucial that the clinician is in no way judgemental or disapproving of the patient's interest or exploration of forms of complementary medicine, as many may be quite interested or may already have experienced other forms of medicine and therapies. What follows are some examples of activities that may assist the patient with unloading of storage and emotions. However, within reason, any technique or activity that takes the patient's mind off their cancer and focusses it on something else is likely to have value.

Stress Management Through Social Therapy

The value of close, social connections and unloading of stress cannot be understated. A prospective longitudinal study of elderly Australians living in community care or residential care carried out over 10 years found that greater networks of friends were protective in terms of decreasing mortality [37]. Research points to the positive value of social support in people with cancer, indicating that it may affect cancer survival favourably ([32, 70, 109]. Having at least one confidant has been found to reduce 7-year mortality by 39% in women with breast cancer, for example [70]. Women who have a strong social network are more likely to survive breast cancer compared with women who are isolated [57]. Some of the key research into social support in cancer is included in Table 2.4.

Going to movies and concerts can be a great escape for a few hours and provide an important circuit breaker from stress and worry in many cases. Group therapy such as cancer support groups may also provide the patient with a sense of not being alone in their experience.

Table 2.4 Research into social support in cancer

• A 6 week structured psychiatric intervention in malignant melanoma patients found significantly reduced levels of psychological distress, greater use of coping methods, and significant increases in % large granular lymphocytes and natural killer (NK) cells with indications of increased NK cytotoxic activity at 6 months [31]. At 5–6 year follow-up, those in the intervention group had a significantly lower rate of death and a trend toward lower recurrence rate compared with the control group. Higher levels of baseline distress and coping, and enhancement of active-behavioural coping over time were predictive of lower rates of recurrence and death [32]. At 10 year follow-up, participation was still significantly predictive of survival [33]
• Research in women with breast cancer has demonstrated a 39% reduction in relative mortality after seven years in those who used at least one confidant in the three months after surgery, and a 46% reduction in relative mortality when they utilised two confidant categories [70]
• An investigation of group support in women with advanced metastatic breast cancer found that the average survival time in those in the group support intervention group (which included improving their ability to express their emotions and learning simple relaxation and self-hypnosis techniques) almost doubled from 18.9 to 36.6 months in comparison to the control group after 20 months of the programme [109]
• A systematic review found that social support and marriage were associated with better breast cancer prognosis [29]
• A study of 9267 breast cancer survivors found that those with small networks (socially isolated) had significantly higher risk of cancer recurrence (hazard ratio 1.43, meaning a 1.43 times greater risk), breast cancer mortality (hazard ratio 1.67) and total mortality (hazard ratio 1.67) than women who were socially integrated. The associations were stronger in women with Stage I and II cancer. In older white women but not other women, lack of a partner and community ties was associated significantly with higher breast cancer-specific mortality. Lack of relatives and lack of friendship ties were both significantly associated with higher breast cancer mortality in non-white women (only) [57]
• Social support in women with ovarian cancer has been found to be associated with greater NK-cell activity in peripheral blood and in tumor-infiltrating lymphocytes [65], and lower levels of vascular endothelial growth factor (an angiogenesis promoter) in tumor tissue and serum [66]

In the Age of Technology and socially networking, research has shown that Facebook users with more friends and more requests to connect live longer [48, 55]. Online social behaviour that indicates face-to-face activity such as posting photos was associated with reduced mortality, however online-only behaviours such as sending messages had a non-linear relationship with moderate use being associated with the lowest mortality [48]. Use of technology, of course needs to be balanced with some of the potential harmful effects of exposure to electromagnetic frequencies (discussed in Chap. 7). The point here is that these positive effects flow on from connecting with other people: that's what is truly beneficial.

Professor Sali tells the story of a Greek gentleman whose family migrated from the Greek island of Icaria to the United States. At the age of 64 he was told that he had cancer and to put his affairs in order. The gentleman sold up his business, and moved back to Icaria, where he proceeded to live a life tending his vegetable garden

and meeting his friends for coffee every morning. This was his informal social therapy where no doubt he unloaded storage of stress and emotions in a supportive atmosphere. Twenty-one years later, he was still going strong, no cancer, tending his veggie patch. Professor Sali, himself once a boy from a tomato-growing town in rural Victoria called Shepparton, refers to this as *Veggie Patch Therapy*.

The key point here is that having someone to share troubles with, and unload stored stress and emotions, is very valuable in patients suffering from cancer and something that the clinician can suggest.

Pet Therapy

Pet Therapy is another form of social therapy, except with a furry friend. Numerous studies have demonstrated the value to health of owning a pet. For example, a study in patients with head and neck cancer undergoing combined radiation and chemotherapy found that assisted pet therapy was associated with significant improvements in social and emotional well-being despite the high symptom burden and expected decreases in physical and functional well-being associated with radiation-chemotherapy treatment [35]. Animal-assisted therapy (using dogs) during chemotherapy has been found to significantly reduce depression of patients and increase their arterial oxygen saturation [88].

Art Therapy

Art therapy encompasses a broad range of therapies including music therapy, dance/movement and various types of art such as painting. It is interesting to note the sudden worldwide popularity of coloring books for adults, which are designed specifically for mind stress reduction. Several studies in cancer patients have demonstrated that art therapy can improve well-being [112]. Research also indicates that art therapy may be effective in decreasing anxiety as well as depression and pain in patients with cancer, and decreasing anxiety in those receiving cancer therapy [7, 60, 80, 112, 115]. Art therapy can be beneficial as a means of expressing emotions when a patient cannot articulate or voice them. Art therapy can be useful for children with cancer who may not be easily able to articulate their feelings.

Meta-analyses indicate that music therapy may have several benefits for people living with cancer, including reduction of anxiety, pain and fatigue and improved mood and quality of life [11, 12].

Table 2.5 sets out some of the evidence of the usefulness of art therapy in patients with cancer.

Table 2.5 Evidence of usefulness of art therapy in cancer

• A meta-analysis of 13 trials found that art therapy (inclusive of music therapy interventions, various types of art therapy and dance/movement therapies) positively affects cancer patient's anxiety, though it did not find a significant effect on depression or quality of life [10]
• Music therapy has been found to decrease anxiety in cancer patients in two systematic reviews [11, 83] (though meta-analysis of one study failed to show a positive effect which may be due to small sample size) [83] and moderately reduce pain in one of these [11]. A later meta-analysis of 22 studies concluded that music interventions may have benefits in reducing anxiety, pain, fatigue and improving quality of life in cancer patients [12]
• Group music therapy of listening to music has been found to improve well-being, relaxation and energy levels, reduce cortisol levels and increase salivary Immunoglobulin A levels [18]
• Mindfulness-based art therapy during treatment in women with cancer has been found to significantly decrease symptoms of physical and emotional distress and significantly increase aspects of health-related quality of life [78]

Recommendation for Art Therapy
Adult coloring books have enjoyed great popularity in the past few years. Coloring in allows the mind to switch off and focus on the now, and may allow negative thoughts to be replaced with positive ones [27]. No special artistic skill is needed. Book and pencils essential!

Writing Therapy

Unloading of stresses including family, work and school problems through writing about them can be very beneficial. Research indicates that writing therapy is associated with improved quality of life in cancer patients and changes in thoughts about their cancer [79].

Studies show that writing for 20 min on each of three days about life stresses produced an improvement in asthma patients within two weeks, and an improvement in joint pain in patients with rheumatoid arthritis at four months in comparison with a group who did not write about life stresses (they received no improvement) [107].

Recommendation for Writing Therapy
It is suggested that patients write in a journal for three consecutive days, then after the first week, once a week for 15–20 min (more often if he or she likes to do so).

Color Therapy

Some people react quite strongly to various colors in their environment. In Ayurvedic Medicine, different colors are associated with the different chakras-energy vortices running along the midline of the body. The color purple or violet is associated with the seventh chakra or crown chakra and has traditionally been associated with healing. In contrast, the color red is more stimulatory in its effect and is associated with the first (base) chakra and is somewhat less calming. In terms of relaxation, wearing colors or having colors within the environment that are calming to the patient can aid in relaxation. Placing a purple colored amethyst stone in the home environment or in a quiet meditation area in the home can also bring a calming quality to the space. The association of colors with chakras comes from the Ayurvedic tradition, though there is much research on the impact of colors on emotions and moods.

Color Therapy Exercise
The color mauve or purple can be very relaxing. A short color therapy relaxation exercise involves drawing a small circle with a yellow highlighter on a piece of yellow paper. After looking at the yellow circle for about 30 s, a violet/mauve halo begins to appear around the circle. The patient should practise this for about two minutes over the next 4 days, then after 4 days, try closing their eyes and retaining the mauve color for 30 or more seconds. The goal is to see if they can do this five times in the one session. This exercise may be done one to three times daily (three sessions per day). Over time, the patient will be able to retain the violet/mauve color for up to half an hour.

Gardening

A systematic review of 22 articles that investigated the potential benefits of gardening for community-living and institutionalised older people found that gardening can promote overall health, quality of life, physical strength, fitness and flexibility, cognitive ability and socialisation [120]. A small qualitative study of ten people with chronic mental illness who engaged in a 6-week group-based gardening activity found that horticulture had an immediate and positive effect on life satisfaction, well-being and self-concept (all components of quality of life) [94].

Meditation

There is a wide body of research supporting the many health benefits of meditation. This includes the benefits of meditation in people with cancer. Dr. Ainslie Meares was one of the pioneers in the meditation field who found that intensive meditation was associated with cancer regression [74]. For example, a study on Transcendental Meditation over eight years found a 49% decrease in the rate of mortality from cancer [104]. Another earlier study of 2000 meditators compared with 600,000 non-meditators found a 55% reduction in tumors. A follow-up over 11 years found 3.3 times fewer admissions for cancer in meditators compared to non-meditators [89].

Benefits of Meditation

Meditation has a number of purposes, including promoting the relaxation response and achieving a greater state of self-awareness. The relaxation response helps undo many of the harmful effects of stress, and incorporates a deeply relaxed physical state with a focused, clear mental state [45]. Some of the physiological benefits of the relaxation response include reduction in blood pressure and heart rate, improved immune regulation and function, reduced platelet adhesiveness, reduced inflammatory and stress hormones, better digestion (increased blood flow, gut motility), changes in brain activity including greater electroencephalogram coherence, increased alpha and theta waves (associated with rest and focus), increased serotonin, reduced reactivity to pain, neural plasticity and neurogenesis, decreased anxiety and depression, increased optimism, and improved coping abilities and resilience [45].

Forms of Meditation

There are a number of different forms of meditation, however essentially they are mental disciplines aimed at regulating the attention [45]. Mindfulness is a term that has gained in use in recent times, typically in relation to meditation, i.e. mindfulness meditation. According to Australian mindfulness meditation expert and medical practitioner and academic Dr. Craig Hassed, mindfulness is simply about awareness [45].

Some forms of meditation utilise a mantra, a word or phrase that is repeated over and over, as a point of focus whilst other techniques focus the attention on the breath. When thoughts arise, the meditator is encouraged to simply observe the thoughts coming and going, like an external observer, bringing the attention back to the breath. In the Progressive Muscle Relaxation (PMR) technique, the idea is to practise letting go of muscle tension in the body [45].

Instructing Patients to Meditate

The clinician may choose to learn some simple meditation techniques themselves, and to practise them in order to gain the benefits of stress reduction themselves, and be able to talk about the benefits to their patients from first-hand experience. The clinician might also feel confident enough to instruct the patient in a simple meditation technique, for example, the PMR technique. This is a simple introduction into meditation and the relaxation response.

Since meditation is often quite new and unusual to many patients and also to their significant others, it often helps to instruct the patient along with their partner or parent or support person, so that this exercise is not foreign to them either. This has a several purposes—the significant other might share in the exercise at home, providing a level of support in sharing the experience, or at the very least not make the patient feel awkward about practising at home. Efforts that the patient makes towards reducing stress, unfortunately, are sometimes not always supported by an often-frightened partner to whom the exploration of experiences such as meditation can be foreign and challenging.

Referring to Meditation Teachers

It is very useful to have a handy reference list of good meditation teachers on hand to give to the patient. Meditation is often easier in a group situation, at least in the early stages of learning, where the meditator can ask questions of the teacher as necessary.

Spirituality and Religion

The benefits of spirituality and religion to people with cancer have been established. Studies of people with cancer have found spirituality and religion to be significantly associated with improvements in subjective well-being and quality of life [13, 38, 58, 102], hope and positive mood states [34, 76], adjustment to cancer [81], management of symptoms [122] and reduced anger-hostility, despair and social isolation [2]. Spiritual well-being has been also found to be associated with lower levels of anxiety in persons with cancer [53]. The challenge of a cancer diagnosis can often be a catalyst for a search for meaning in life and for some, provides the impetus to make changes to their life.

Multimodality Programmes

Lifestyle interventions can improve immunity and health and assist those with cancer. Australian research has been conducted into a lifestyle programme (conducted by the Gawler Foundation, a support centre for people with cancer) which

incorporates meditation, social support, positive thinking and a vegetarian diet in a cohort of predominantly women with cancer. The study found beneficial effects of the programme, conducted over 3 months, on mood, coping and quality of life (QOL). Spiritual well-being was, in particular, linked with improvement in QOL. The finding that programme was particularly beneficial in those with low QOL and emotional well-being may be largely due to the effects of meditation in reducing anxiety and increasing spiritual well-being [98].

The Ornish lifestyle programme was trialled in 80 men with prostate cancer who had chosen to wait and watch rather than undergo treatment. The lifestyle programme incorporated dietary recommendations (including dietary supplements of fish oil, Vitamin E, Vitamin C and selenium, plus a diet low in fats [in particular saturated fats and animal fats], and that included vegetables/fruits/wholegrains, legumes and soy products), exercise (30 min walking, six times per week), stress management (yoga, meditation, breathing and PMR) and attendance at a support group one hour per week. Forty men were in the treatment group and 40 in the comparison group (usual lifestyle). A year later, six of the 40 men in the usual lifestyle group developed aggressive cancer whereas none in the Ornish lifestyle programme did. In addition, the mean PSA level in the Ornish programme group decreased 4% in comparison to the control group (usual lifestyle) which increased an average of 6% [90].

Tai Chi and Qi Gong

Variously described as meditation in movement, the Chinese art/exercise forms of tai chi (also referred to as tai chi chuan or taijiquan) and qi gong incorporate slow, controlled movements with breathing to help still the mind and circulate the qi, or energy, around the body. Originally based on observations of movements of animals, tai qi movements are essentially martial arts movements, though in practise the martial arts applications of the various movements are not always taught. There is evidence that regular tai chi is can cause changes in the Th1 and Th2 immune responses which are associated with immune modulation of Natural Killer T-cells and Dendritic Cells and their reciprocal interactions [62]. Other reported benefits include increased strength and flexibility, improved sleep, reduced pain and anxiety, reduced depression, improved general stress management, improved self-efficacy and exercise self-efficacy, better balance and less falls, and increased cardiopulmonary function [61, 121]. A meta-analysis demonstrated that tai chi had a significant effect on reducing depression [121]. In cancer patients, a systematic review and meta-analysis of nine randomised controlled trials found that qi gong and tai chi had positive effects on cancer-specific quality of life, as well as fatigue, anxiety, immune function and cortisol levels [123].

Others

There are several other activities or therapies which may be useful in reduction of stress an unloading. These include hypnosis, cognitive behavioural therapy, breath work and exercise (see Chap. 6 on exercise). The reader is referred to other sources for a description of these.

Conclusion

The science behind the impact of stress on the human is becoming well elucidated. There is compelling evidence that storage of stress plays a part in the pathogenesis of cancer, and that the immune system, endocrine system, nervous system and the gut are all involved. In the Ultimate Consultation, by explaining at a basic level how storage of stress and emotions impacts on the various systems of the body, the patient may come to understand how stresses in their life may have contributed, along with other factors, to imbalance in their body that has manifested as cancer. If they can understand this, then they are in a better position to also see how they can make changes that can affect these body systems in a positive way, leading them back to better health. A healthy patient will always do better than an unhealthy one, no matter what the illness.

By discussing various options with the patient about how they might reduce stress (as part of a holistic approach that considers other factors including diet and exercise), the clinician can open up a different way of being to the patient that they may not have considered before. The goal is empowerment of the patient to become the Ultimate Patient, one who is proactive in taking charge of their health. The Ultimate Result really does depend on the Ultimate Patient.

Summary: Key Points About Storage of Emotions and Stress

1. There is clear evidence of an association between stress, depression, anxiety and cancer and that stress is implicated in cancer initiation and progression.
2. Depression, stressful life events, social isolation and lack of social support have been linked with poorer outcomes in cancer patients.
3. Constraint of emotions and low levels of emotional expression are associated with poorer survival in those with cancer.
4. Stress not only involves the HPA axis and the immune system—research indicates the gut microbiome plays a major part in the stress response, and there is increasing evidence that the bacterial microbiota plays a key role in carcinogenesis.

5. Stress reduction and social support have been shown to improve physiological functioning in the body and improve outcomes in patients with cancer.
6. Any technique or activity that takes the patient's mind off their cancer and focusses it on something else is likely to have value.

Summary: Key Techniques for Unloading Stress
Unloading of stored stress can be done in many ways including the following:

- Stress management through social therapy
- Pet therapy
- Art therapy
- Writing therapy
- Color therapy
- Gardening
- Meditation
- Spirituality and religion
- Multimodality programmes
- Tai Qi and Qi Gong
- Others.

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Chapter 3
Nutrition

Let thy food be thy medicine and thy medicine be thy food.
Hippocrates.
In Chinese medicine, diet therapy is the highest form of medicine.
Various Chinese medical texts.

In this chapter we explore the following:

- Evidence of an association between diet and cancer
- Cancer risk factors associated with diet including obesity and diabetes
- How foods can heal, including their effects on cancer pathogenesis
- Incorporating dietary advice into the Ultimate Consultation
- 14 Key Dietary Principles including foods to include and foods to avoid.

Introduction

We are what we eat. From both the ancient Greeks and the ancient Chinese (and of course many other cultures), we receive the same wisdom—food is a source of medicine. We are alive because of the various food sources available to us, at a very basic level. But that doesn't mean we are all alive and well.

For people with cancer, ensuring that the foods eaten on a daily basis are good foods is very important to give them the best possible chance of overcoming cancer. A healthy patient will do better than an unhealthy one and good nutrition is one of the essential pillars of health, along with stress reduction, exercise, sunlight and sleep. The practice of mindfulness and daily creative sessions are also very important. If a person is not feeling good about themselves, however, they probably won't choose good foods, so it is vital that the patients address stress and unload it. The mind–body connection is extremely important, as you can see from just some of the evidence about stress and cancer in Chap. 2.

Cancer is reflective of a state of imbalance within the body. Poor food choices can set up a pro-inflammatory state systemically, and systemic inflammation is part

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of the pathogenesis of cancer, as well as many other chronic diseases. Good food choices can assist by first not adding to the inflammatory process, and second, may help counteract many of the pathways involved in the pathogenesis of cancer.

Our earth has provided us with the means to achieve wellness. Many plant foods found in nature have anti-cancer properties: the scientific evidence of how particular foods and/or the active constituents within them interrupt the various pathways involved in cancer is established and growing. Plants have many potentially active constituents within them which act synergistically and likewise the combination of certain foods can have a synergistic effect. The emphasis therefore should be on a healthy and balanced diet.

In This Chapter

This chapter will look first at some of the evidence of an association between diet and cancer, as well as evidence of associations between particular diets and better health outcomes. The evidence of an association between overweight and obesity and cancer is then examined, before then looking more closely at cancer pathogenesis, to understand how foods can address many of the events involved in cancer. We will then discuss 14 Key Dietary Principles, encompassing foods to avoid and foods to add to a patient's diet.

In this book, we will cover some of the basics of diet and nutrition only. For more in-depth discussions, readers are referred to the many good books on nutrition that are available such as David Wilkinson's *Can Food Be Medicine Against Cancer* and Kenneth Block's *Life Over Cancer*. Pieces of wisdom from the ancient Chinese that pertain to diet as well as life more generally can be found in Peter Deadman's book *Live Well Live Long*.

Evidence of the Association Between Diet and Cancer

The figures may differ a little from publication to publication, however, it has been estimated that only 5–10% of cancer is due to genetic defects. Up to 30–35% of cancer-related deaths are estimated to be linked with diet, 25–30% are due to smoking, 15–20% due to infections and the rest due to other factors such as stress, physical inactivity, radiation, and environmental pollutants [7]. Even if a person has a genetic defect that may increase risk of cancer, by protecting themselves with a healthy lifestyle and diet, the disease won't necessarily manifest.

The link between diet and cancer has been revealed by findings of a large variation in cancer rates between countries and correlations with diet and observations of changes in cancer rates with migration [7, 42]. When people migrate from countries known to have low rates of specific cancers (such as Asian countries where the incidence of prostate cancer is 25 times lower and rate of breast cancer 10

times lower) to countries with high rates, adopting the diet and lifestyle of the new country of residence, cancer rates in these people increase substantially [7].

Evidence of Protective Effects of Particular Diets Against Cancer

Studies on Diets High in Vegetables and Fruits

There is substantial research that indicates the protective effect of diets high in vegetables and fruit against cancer and their role in the prevention of disease recurrence [33, 42, 58, 153, 164, 217, 218, 241]. See Table 3.1 for some examples. However, it is important to be aware that there have also been many studies which have not found an association between diets high in vegetables and fruits, or low in fats, with cancer. These might seem counterintuitive to common sense; however, the individual studies need to be interpreted carefully, and the diets of study populations scrutinised. As argued by Campbell and Campbell [42], some large studies which have investigated the relationship between particular dietary factors and cancer risk have made erroneous conclusions because their study populations were

Table 3.1 Studies that support positive impact of vegetables and fruit

• The Iowa Women's Health Study of almost 42,000 middle-aged women found that consumption of all vegetables and fibre were inversely associated with risk of colorectal cancer, with a 27 and 20% reduced risk comparing the groups with highest intake with lowest respectively [241]
• High consumption of vegetables, particularly cruciferous vegetables (though not fruit), was found to be associated with a reduced risk of prostate cancer [58]
• The Black Women's Health Study found that total vegetable intake was associated with a significantly decreased risk of oestrogen-negative/progesterone-receptor-negative breast cancer (though not overall breast cancer risk) and there was a non-significant trend of an inverse association between breast cancer risk and intake of cruciferous vegetable intake and carrot intake [33]
• Increased fruit and vegetable consumption was associated a greater recurrence-free survival in women with breast cancer, as measured by the biomarker plasma carotenoids [218]
• A review of observational cohort studies (1985–2002) found that there was a positive association between intake of vegetables, fruit and their micronutrients and survival in five of eight cohort studies of breast cancer survivors [217]
• Another study of 1901 early-stage breast cancer patients that women following a diet characterised with high intakes of fruits, vegetables, whole grains, and poultry had statistically significant decreased risk of overall death as well as death from non-breast cancer causes [153]
• A population-based cohort study of 609 women with epithelial ovarian cancer who were observed for up to 5 years found a significantly reduced risk of death in women who had a higher intake of vegetables before diagnosis (25% reduction) and higher intake of cruciferous vegetables [180]

eating diets high in animal-based foods (even though low in fat) and the studies were trying to hone in on one nutrient or food at a time [42]. The limitations of scientific research must be borne in mind—if studies are not well set out, the inherent reductionist nature of research may miss important findings. Whole dietary patterns are more likely to be much more important.

Vegetarian Diets

Epidemiological studies indicate that those on vegetarian diets, in particular vegan diets, tend to live longer than meat-eaters. A study of Seventh Day Adventists found that there was a 12% reduction in risk of death from all causes in vegetarians compared with non-vegetarians [194]. An earlier study in 34,192 Seventh Day Adventists found that cancers of the colon and prostate were significantly more likely in non-vegetarians (increased risk of 88% and 54% respectively). Also, those who ate meat frequently had a higher risk of bladder cancer [102]. In addition, the intake of legumes was negatively associated with risk of colon cancer (in meat-eaters) and risk of pancreatic cancer, and higher consumption of all fruit or dried fruit was associated with decreased risks of lung, prostate, and pancreatic cancers [102]. However, what also needs to be considered here is the social/family therapy provided within close-knit communities, as this might be just as important as the foods eaten.

Mediterranean Diet

The Mediterranean Diet is also known to be associated with better health outcomes including reduced total mortality and cardiovascular disease risk [26]. A review of observational studies indicated that it is probably protective against cancer also [263]. The diet is characterised by a high intake of olive oil and low intake of saturated fats, high consumption of fruit, vegetables, nuts, cereals and legumes (that in the past were largely unrefined), moderate consumption of ethanol (mostly as red wine at meals), moderately high consumption of fish (depending on proximity to the sea), low consumption of meat and meat products, and low-moderate intake of milk and dairy products (and then mostly in the form of cheese and yoghurt) [253].

The European Prospective Investigation into Cancer and Nutrition (EPIC) study investigated the dietary, lifestyle and other characteristics of more than half a million people in Europe before a diagnosis of cancer or another chronic disease. The study of 25,623 Greek men and women found that not only were there benefits of adopting the diet in terms of a significantly reduced incidence of cancer, but even adopting some aspects of the diet was sufficient to lower the incidence of cancer. The closer the adherence to the diet, the lower the incidence and risk of cancer.

What was very interesting was that although the Mediterranean Diet was strongly and inversely associated with cancer risk, when they examined the association between the individual components of the diet, they did not find any significant associations between these and cancer risk. This could suggest that there are synergisms between the components of the diet that are important (though other explanations relate to how data is combined in research) [26]. Other studies have also found that a high degree of adherence to this diet is associated with significantly lower mortality from cancer as well as coronary heart disease [253].

Lessons from 'The China Study'

The China Study was a correlation study of women and men living in 65 counties in 24 provinces of rural China. It stands as one of the most significant ecological studies in nutrition of the twentieth century, led by eminent researcher Dr. T. Colin Campbell. Some of the findings of this study, together with research from other sources that are published in the book entitled *The China Study* (Wakefield Press), provide evidence-based arguments that a diet high in animal-based foods is implicated in particular cancers. They also remind us of the methodological shortcomings of much of the research into nutrition which has focussed on individual nutrients or foods rather than examine diet in the more holistic sense.

A startling difference was found between rural China and the typical western diet in the U.S. The rural Chinese diet had less fat (14.5% of calories in rural China vs. 34–38% in the US), more dietary fibre, more iron, and less total protein. In rural China, 9–10% of total calories were consumed as proteins, with only 10% from animal-based foods (the majority coming from plant sources of protein). In contrast 15–17% of total calories of the American diet were from protein, and more than 80% of it was from animal sources. What was extremely interesting was that the rural Chinese diet, high in plants and low in animal protein, was *higher* in total calories than the U.S. diet, yet they were slimmer—average body mass index in rural Chinese was less than in the U.S. and this wasn't explained by differences in physical activity [42].

The Social Context of Eating Is a Missing Link in Research

What is missing from studies on diets such as the Mediterranean Diet is consideration of the context for eating. The Mediterranean Diet is not perfect—it contains preserved meats, recently pronounced as carcinogenic, and there are cakes and ice creams in the mix of what is eaten too (the latter are not listed as features of the diet however). What is likely to also be protective is the family structure that provides the context for eating in these cultures and regions of the world. Perhaps it is the

social support that eating within a family environment that is more important? The social context of eating may be healing and protective in itself. It may even compensate for some of the poorer food choices. We won't know for sure until we have a 'university study', but we can hypothesise.

Happiness is contagious and can positively impact on others. The Framingham Heart Study found that a friend who becomes happy and who lives within about 1.6 km (one mile) of another person increases the chance that the other person is happy by 25%; the effect is even greater (42%) when the friend lives within half a mile (0.8 km). Similar effects were found in relation to siblings who live within a mile (14% increase) and next door neighbours (34%) [103]. The positive changes that can occur within the immune system of people in the company of others, and other factors including Vitamin D levels, physical activity level and other behavioural factors are rarely considered in research designs, yet arguably they need to be. Research designs do need to consider foods and nutrition within a broader behavioural and social context. Food for thought (pardon the pun).

Key Points:

- The social context of eating may be healing and protective in and of itself
- Research needs to consider the social contexts of eating and the potential impact on health.

Overweight, Obesity and Cancer

Overweight and obesity are risk factors for cancer, diabetes and Metabolic Syndrome (which are themselves risk factors for cancer), development of insulin resistance (visceral adiposity), as well as hypertension, stroke and coronary heart disease [27, 115, 178, 184]. Many cancer patients are overweight and therefore may have co-morbidities. Addressing weight, through healthy food choices, is likely to have many health benefits and this will be discussed later in the chapter.

Stress and Weight

It's important to remember that if a person is overweight or obese, there are usually a multitude of actors involved. For example, if someone is stressed, they may eat more, leading to increased cortisol being released into the bloodstream, as well as insulin. Figure 3.1 shows some of the factors that may be involved:

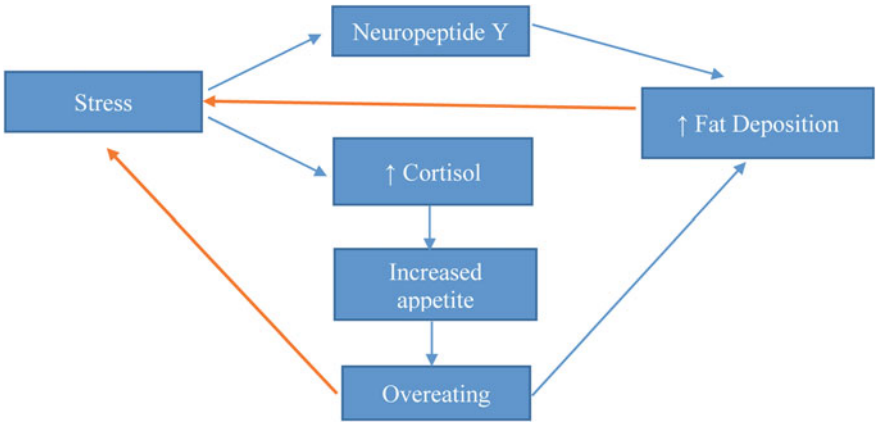

Fig. 3.1 Stress and overweight

The Link with Cancer

Being overweight or obese is a risk factor for cancer occurrence. In the year 2000, obesity was estimated to contribute to an estimated 14% (men) and 20% (women) of cancer-related mortality in the U.S. [40]. In 2007, an estimated 34,000 new cases in men (4%) and 50,500 new cases in women (7%) were due to obesity [182]. Body mass index (BMI) is significantly associated with higher death rates due to the following cancers: oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma and multiple myeloma. There is a significant trend of increased risk of death with increasing BMI for cancers of the stomach and prostate in men and breast, uterus, cervix, and ovary in women [40].

Cancer sufferers who are obese tend to have poorer outcomes in terms of increased risk of all-cause mortality and cancer-specific mortality [182]. Those with a body mass index (BMI) of at least 40 have been found to have death rates from all cancers combined that are 52% and 62% higher for men and women respectively compared to those of normal weight [40].

Breast cancer

Women with breast cancer who are overweight or obese are significantly more likely to die of breast cancer than lean women [272]. Women who are obese at breast cancer diagnosis have a 33% higher risk of recurrence and mortality compared with women who have normal weight [209]. Several observational studies have found an association between post-diagnosis weight gain and higher risk of recurrence and mortality which was independent of BMI at the time of diagnosis [34]. In women with Stage 1–3 breast cancer, being overweight or obese has a negative impact on recurrence-free survival, overall survival and breast cancer-specific survival; diabetes also has a negative impact on overall survival and

recurrence-free survival [137]. Overweight and obesity also increase the likelihood of progression including metastasis in triple negative breast cancer following surgical resection [54].

Postmenopausal breast cancer survivors who were overweight or obese had higher levels of sex hormones (estrone, estradiol, testosterone) than lighter women, providing a potential link between adiposity and breast cancer [173]. Overweight and obesity and lack of physical activity are all associated with increased inflammatory markers including CRP, interleukin-6, interleukin-1, serum amyloid A and tumor necrosis factor α [129, 205]. Inflammation is a key part of the cancer terrain.

More than 65% of breast cancer survivors are overweight or obese [137], and unfortunately the majority of women who are in the normal weight range gain weight after diagnosis [262]. This is clearly not something that is desirable.

Metabolic Syndrome and Diabetes as Risk Factors for Cancer

Metabolic Syndrome is a risk factor for several forms of cancer including liver, colorectal, and bladder cancer in men, and endometrial, postmenopausal breast, rectal and colorectal in women [87]. Diabetics have a higher risk of several cancers including pancreatic, liver, breast, colorectal, kidney, bladder, endometrial and breast cancer and non-Hodgkinson's Lymphoma, and mortality is also increased [265].

In one study of women with early-stage breast cancer, women with the highest fasting insulin levels had approximately twice the risk of distant recurrence and over three times the risk of death compared with women in the lowest fasting insulin group, and the effect of insulin on survival was independent of body mass index [109].

Insulin resistance has been implicated in the pathogenesis of cancer: chronically elevated insulin can lead to tumor growth [41] and insulin resistance has been linked to breast cancer development [139, 243]. When insulin is elevated, it leads to increased IGF-1. IGF-1 and insulin, which are both understood to be growth factors, then down-regulate apoptosis and promote cell division [126]. Elevated fasting insulin levels have been found to be associated with distant recurrence and death in women with early breast cancer; insulin has been found to be correlated with body mass index, which in turn was found to be significantly associated with distant recurrence and death [109].

Benefits of Weight Loss in Cancer

There is clear evidence of benefits of weight loss in cancer and risk factors for cancer. Weight loss, through lifestyle approaches that combine changes to diet and increased physical activity, can have important health benefits on some of the risk factors for cancer that may also be co-morbidities (e.g. insulin resistance, Metabolic

Table 3.2 Weight loss benefits for cancer and cancer risk factors

• A recent review found that several weight loss and exercise programs in healthy women as well as breast cancer survivors were associated with reductions in insulin levels of 10–30% [130]. This is important since lowering of insulin by 25% has been found to be associated with a 5% absolute improvement in breast cancer mortality [109]
• The Women's Nutrition Intervention (WIN) Study, though not specifically investigating impact on weight, found that a low fat diet was associated with significantly reduced weight loss and decreased breast cancer recurrence in women with breast cancer. The effect on breast cancer recurrence was stronger in women with estrogen-negative breast cancer. Other mechanisms are likely to be involved in breast cancer (other than sex hormones) including adipokines, IGF-1, insulin resistance and inflammatory biomarkers [31]
• A study of physical activity and caloric restriction intervention in healthy postmenopausal women found that lower caloric intake as well as physical activity and lower body mass index were all independently associated with significantly lower mean fasting insulin levels [51]
• A study showed that insulin resistance has been found to improve significantly after weight loss, albeit via gastric band surgery [120]
• The Diabetes Prevention Program study of people at risk of diabetes investigated the impact of a lifestyle intervention program that included a weight reduction goal and physical activity. Those in the lifestyle intervention group had significantly greater weight loss than the two control groups and that they developed significantly less diabetes (incidence reduced by 58%) at the end of the study than the Metformin Group (incidence reduced by 31%) or the placebo group. Both lifestyle intervention and Metformin were associated with lower blood glucose levels after one year (Diabetes Prevention Intervention Group 2002)

Syndrome and diabetes), and on some of the underlying cancer pathways involving insulin and IGFs. See Table 3.2 for some of the studies.

Caution needs to be taken however: sudden weight loss in cancer patients may increase the risk of clinical deterioration, possible due to the effects of increased metabolic end-products and nutrient depletion.

How Foods Can Heal

As mentioned previously it has been estimated that up to 30–35% of cancers are linked to diet [7]. This is worth remembering, as it means quite a lot of cancer can be prevented through healthy food choices.

Dr. T. Colin Campbell and his colleagues originally conducted studies in rats to investigate the impact of animal-based foods including dietary protein on the initiation and promotion of cancer. These and other animal studies indicate some very important findings in relation to diet and cancer pathogenesis including the following:

- Nutrition is far more important in controlling cancer promotion than the dose of the initiating carcinogen
- Nutrients from animal-based foods (including casein in milk) increased tumor initiation and development and nutrients from plants decreased their development

- A plant-based diet encourages more physical activity and discharges calories as body heat instead of storing them as body fat [42].

Whilst these studies are in animals, nonetheless they are helpful in understanding how diet can impact the development of cancer which might be applicable to humans. See the book *The China Study* [42] for some very interesting reading.

Foods Acting on Pathways Involved in Cancer Pathogenesis

There are specific foods and their active constituents that have an action on the pathways involved in cancer pathogenesis, including cancer metabolism, cell cycle control, apoptosis, inflammation, hormonal balance, angiogenesis and metastasis [252]. Some foods can assist by boosting the immune system, whilst others work as protective food chemicals. The specific actions of particular foods in relation to cancer pathogenesis will be discussed throughout this chapter.

Plants as Antioxidants or Modulators?

What is not well understood is that plants and some of their active constituents are able to modulate various activities within the body. For example, cocoa can enhance the function of normal cells but destroy cancer cells [138]. Omega-3 oils in fish, for example, can enhance immunity in persons with depressed immunity, and can normalise or modulate hyperactive immunity in people with allergic conditions or autoimmune disorders [143].

Research is now showing that nutrients that have previously been thought to act as antioxidants are actually acting in a different way in protecting the body against, or combatting cancer. For example, Vitamin C has traditionally been known of as an antioxidant; however, it has been shown to be able to destroy cancer cells in vitro without neutralising the efficacy of chemotherapy and in human studies [32]. Here Vitamin C is clearly not acting as an antioxidant under these circumstances. Vitamin E has also been shown, in vitro, to assist in the destruction of cancer cells when irradiated (whilst helping to preserve normal cells). Antioxidants are discussed in more detail in Chap. 7.

An Alternative Theory of Carcinogenesis and Implications for Diet

Before we turn to how to incorporate dietary advice into an integrative consultation, it's worthwhile noting what is considered the dominant theory of carcinogenesis, and describing (very briefly) another theory that has been forming for many decades

that challenges it, for it does have some implications for diet. The Somatic Mutation Theory of Cancer which has dominated the last one hundred years of scientific research into cancer posits that cancer is primarily due to genetic mutations. The 'Metabolic Theory of Cancer', originating with Warburg and later developed further by others including Pederson and more recently Seyfried [233], posits that cancer is a metabolic disease first and foremost, rather than a genetic disease. According to this theory, the mitochondria have become damaged, leading to defective respiration. Genetic mutations occur downstream from this event, not prior to it. Seyfried sets out convincing scientific evidence that in cancer cells, the mitochondria have become damaged and fewer in number, and instead of using the oxidative phosphorylation pathway, utilise the less efficient glucose fermentation pathway [55, 232, 233]. This theory fundamentally challenges the direction of oncology research which has primarily focused on trying to understand and characterise genetic mutations. It also has profound implications for metabolic therapies that could be developed.

The 'Ketogenic Diet' was developed on the basis of this theory. The diet is characterised by caloric restriction, low in carbohydrates and protein, and the rest of the diet consisting of fats. The justification for this is that cancer cells have a high need for glucose, and when glucose is restricted, the cancer cells are forced to compete with healthy cells for available glucose. Healthy cells are able to switch to burning ketone bodies, but cancer cells are unable to, which creates metabolic and oxidative pressure [55]. Pre-clinically and in case studies, there is evidence that the diet can slow tumor growth [55].

For more information readers are referred to two excellent books, *Tripping Over the Truth: the Return of the Metabolic Theory of Cancer Illuminates a New and Hopeful Path to Cure* (Travis Chistofferson), an easy read, and for the serious science, *Cancer as a Metabolic Disease* (Thomas Seyfried) (see Reading Recommendations at the end of the book).

There are, of course, many other diets that have been devised for cancer sufferers. Readers are referred to other sources for information on these. We will now examine what kinds of information may be included in discussions with cancer patients in relation to eating and foods.

Incorporation of Dietary Advice into the Ultimate Consultation

There are a few simple goals in the Ultimate Consultation when it comes to nutrition:

- Goal 1: Sharing information on the role of eating and diet in health
- Goal 2: Finding out what the cancer patient habitually eats
- Goal 3: Sharing information about foods to avoid and foods to include in the diet.

It is suggested that you put any dietary advice in writing (e.g. as part of a Wellness Plan) and review within 3 months. Generally, people forget most of what they have been told within 3 months [212]. Professor Sali gives his patients printed notes to take home with them, summarising key information and giving them sample breakfast, lunch and dinner ideas. In addition, it's wise to remember that dietary changes should be doable: if changes are too difficult to make due to unaffordability or lack of access to particular foods, or if diet recommendations are too rigid, this can add stress to the patient. This is not desirable. The changes should be able to be sustained—rigid diets can simply make people miserable and be counterproductive. Finally, in the end the patient has to be responsible for making changes.

Key Points About Dietary Advice

- Put any dietary advice in writing and review within 3 months
- Dietary changes should be do-able and sustainable
- The patient is responsible for making changes to diet.

Goal 1. Sharing Information on the Role of Eating and Diet in Health

The first part of this chapter set out evidence in relation to how diet might impact both positively and negatively in relation to cancer. Some of these general facts and figures could be shared with the patient, emphasising what positive changes can be made going forward that will assist the patient in achieving better health overall. Here are some general topics that you could start with, before getting into discussions about specific foods:

- **How the mind–body connection comes into play in eating**: The importance of the mind–body connection in association with eating habits can also be discussed, including how stress can lead to unhealthy eating habits such as overeating or making poor food choices. Generally speaking, if a person is not feeling good about themselves, they will probably not make healthy choices about food. They may also use food as a means of comforting themselves, contributing to overeating. Thus, the root cause of stress and unhappiness needs to be addressed.
- **Changing diet is about forming new, healthier habits**: Diets are habits and often simply repetitions of cultural and/or family patterns. Changing diet is about practising eating those foods that are most beneficial for health. Making changes will take discipline, not unlike the discipline of athletes or sportswomen/men and their commitment to training.

- **Relationship between overweight/obesity and cancer**: Where relevant, the relationship between overweight/obesity and cancer outcomes, plus other diseases that are risk factors for cancer (e.g. diabetes, Metabolic Syndrome) can be discussed, again with an emphasis on what positive changes can be made to achieve more favourable outcomes. It may be useful to mention some facts and figures from studies that have demonstrated the benefits associated with weight loss (Table 3.2), as this may help motivate the patient to make changes.
- **Why good food is important during chemotherapy/radiation therapy**: If the patient is going to undergo chemotherapy or radiation therapy, they should be advised that it is important no additional stresses are placed on the body by ingesting foods that set up pro-inflammatory conditions. People receiving chemotherapy or radiation therapy are already receiving a toxic insult to their bodies, so it is important not to add further toxicities through poor food choices.
- **Why the context of eating is important**: An important aspect of healthy eating is the context within which it is done. When eating can be done in a relaxed atmosphere, with loved ones, there are the added benefits of social therapy that can be tremendously positive. The health benefits of diets such as the Mediterranean Diet are likely to be as much about the context of eating within a family support system as some of the foods eaten, though this aspect of nutrition, the context of eating, is not something that is investigated in most of the published studies on nutrition. Yet, it is likely to be very important. Eating with someone can be a good opportunity for important unloading of stress.
- **How foods can address some of the cancer pathways**: The clinician can share some basic information about the underlying processes involved in cancer pathogenesis, and how foods are able to assist in addressing some of these processes. Again, by empowering patients with basic information, it gives them essential knowledge as to how and why making changes to diet might benefit them.

Goal 2. Finding Out What the Patient Habitually Eats

In the consultation, it will be important to understand a patient's food habits which can be done simply by asking the patient what they usually eat, as a rule, for breakfast, lunch and dinner. Also, you can ask them whether they skip meals, what they snack on, what beverages they have daily and how many cups approximately (which will give you an idea of liquid intake). For more details, you can ask the patient to complete a 5-day diet diary in which they record everything they eat and drink for 5 days, including at least one day on a weekend (since diets can change on weekends). Frequency of consumption of foods that are unhealthy, including fast foods is important: eating an occasional fast-food meal is unlikely to be

problematic; however, eating them frequently and in large quantities will most certainly be and will most likely lead to weight gain plus changes within the body that can contribute to cancer (and other disease) pathogenesis.

Completing a diet diary is, in and of itself, educational for patients and that itself may encourage learning and change. What we eat is largely habitual, usually forged over a lifetime and often following family patterns of eating. Changing diet means changing habits and practising a new habit, one that is healthier. The key is to empower the patient with information and the knowledge that they can change.

Key Points

- If a person is not feeling good about themselves, they are more likely to make poor food choices. The root cause of stress and unhappiness needs to be addressed.
- Completing a 5-day diet diary is educational and may encourage learning and change.
- Diet is habitual. Changing diet means changing habits and practising a new habit, one that is healthier. This will require discipline.

Goal 3. Sharing Information about Foods to Avoid and Foods to Include in the Diet

In beginning a conversation about what foods can be added to diet and which ones to avoid the clinician can begin with talking about some overarching dietary recommendations. Key recommendations from the *World Cancer Research Fund and American Institute for Cancer Research Second Expert Report* [276] include the following:

- Eat mostly plant-based foods
- Limit intake of red meat and avoid processed meat
- Limit consumption of energy-dense foods and avoid sugary drinks
- Limit consumption of salt
- Avoid mouldy cereals and legumes/pulses.

Then one can move on to talking about 14 Key Dietary Principles, set out in Table 3.3, working through each of these systematically. Professor Sali has printed patient notes that summarise most of these principles that he gives to the patient to take home with them. He uses these as a framework to work through information about diet.

The remainder of this chapter will focus on each of these 14 Dietary Principles.

Table 3.3 Fourteen dietary principles

1. Eat regularly and enjoy meals
2. Eat organic foods where possible and avoid genetically modified foods
3. Eat a rainbow diet of colorful foods, with plenty of fresh vegetables and fruit daily
4. Limit red meat
5. Incorporate healthy dairy products
6. Reduce overall consumption of (unhealthy) fats
7. Consume healthy fats and oils and avoid unhealthy ones
8. Keep hydrated but choose your drinks wisely
9. Avoid excess sugar, artificial sweeteners and salt
10. Avoid foods containing acrylamides
11. Eat dark chocolate
12. Eat for your gut microbiome
13. Avoid foods that interfere with sleep
14. Pay attention to food cooking and storage methods

Principle 1: Eat Regularly and Enjoy Meals

When a person has cancer, it is prudent to remember, particularly when there is cachexia or when they are undergoing treatment such as chemotherapy that appetite is disrupted and nausea may be prevalent. It is important that eating is perceived as enjoyable, as much as is possible under the circumstances. Adhering to strict diets, however, nutritionally justifiable (and many are not) may simply be counterproductive if the poor person is miserable. Sometimes too much emphasis can be placed on diet to the point that the person and their loved ones living with them are stressed out about food. We think that this is counterproductive.

As much as possible, meals should be regular and eating should be done in an atmosphere that is not rushed, and allows for plenty of time to chew (an important and often neglected part of the digestive process), bringing people together in a positive atmosphere (social therapy). The coming together over a meal is an opportunity to relax, enjoy company and unload stresses and the positive benefits of this should not be underestimated. A study found that when people were paired up and fed various foods, when they ate the same foods, rapport was better [274].

For those with poor appetite and/or nausea (which can be the experience of those having chemotherapy), including ginger in the meal or having a cup of ginger tea 30–60 min prior to meals can help improve appetite.

Principle 2: Eat Organic Foods Where Possible and Avoid Genetically Modified Foods

Where possible, organic foods are vastly superior to non-organic foods for a few reasons. First, there is evidence that they contain higher amounts of nutrients. Second, organic foods don't contain the added pesticides and other contaminants

that most commercially grown fruit and vegetables have which can add a toxic load to the body [21].

A recent review of nearly three decades of epidemiologic research (44 papers) on the relationship between Non-Hodgkin Lymphoma (NHL) and occupational exposure to agricultural pesticides found that several herbicides and insecticides were positively associated with NHL and two herbicides were associated with a subtype, B Cell Lymphoma [227]. Whilst occupational exposure in the agriculture industry is arguably different to the kind of exposure through eating foods that have been sprayed with pesticides, this nonetheless should sound a cautionary bell.

The Danger of Genetically Modified Organism (GMO) Foods

Genetically modified organism (GMO) foods are a recent phenomenon and whether they can cause cancer in humans is not substantiated (yet); however there is concern about their potential to cause harmful effects on the body. The major debates on health concerns around GMOs are based on theoretical considerations and animal experiments [72]. The problem has been that there are no epidemiological studies (human or animals) to support a claim either way, and part of the issue is that there is a lack of labelling and therefore sources of evidence in GMO-producing countries [72].

Major cultivated GMO foods are soy, corn and oilseed rape or canola. These plants have been modified genetically to tolerate and/or produce one or more pesticides, and contain residues of these (most of which are Roundup residues, a major herbicide used throughout the world) [72]. Table 3.4 sets out foods most and least prone to contamination with pesticide residues.

Animal research has shown that three different types of genetically modified maize were associated with signs of hepatorenal toxicity in rodents, and effects on the heart, adrenal, spleen and blood cells were also found [71]. A controlled study in which 200 rats were fed with maize treated with Roundup or Roundup-contaminated water for 2 years found that the rats had disturbances in liver and kidney biochemical markers and testosterone and estradiol levels at 15 months, and at the end of the study, hepatorenal deficiencies and female

Table 3.4 foods more and least prone to contamination with pesticide residue

Foods prone to contamination with pesticide residue	Foods least prone to retaining pesticides
Celery, cucumbers, tomatoes, cherry tomatoes, capsicum, cucumbers, snap peas, potatoes, hot peppers, spinach and kale, and the following fruit: apples, strawberries, peaches, grapes, cherries and nectarines [85, 273]	Avocados, sweet potato, cauliflower, cabbage, eggplant, asparagus, sweet corn, peas, sweet peas, asparagus, eggplant, and onions (broccoli is also considered reasonably clean) and the following fruit: grapefruit, cantaloupe, honey dew melon, pineapples, mangoes, paw, and kiwi fruit [86, 273]

mammary tumors (3.25 more than the control group at 700 days) associated with premature death [229].

The evidence about GMO foods is slowly gathering. We know herbicides/insecticides are poisons and there is some indication of serious adverse effects in animal studies. Thus, it is best to avoid GMO foods where possible, particularly when one has an illness such as cancer. This is of course made more difficult if food products are not labelled as to whether or not a product contains GMO foods or not. It is thus incumbent on all of us to put pressure on our own governments to change this.

Switching to Organic Foods

As much as possible, patients should try to make the switch to organic foods. However, these are more expensive in general, and not as readily sourced. If it is not possible to switch entirely to organic foods, an option may be to choose to buy organic those vegetables that are more prone to chemical contamination. Another option is to buy as organic foods those foods that are readily available and therefore there probably won't be as much of a price differential (between organic and non-organic). If organic foods cannot be purchased, patients should be advised to wash vegetables and fruits carefully. This will, at least, remove some of the contaminants on the surface of the vegetables and fruits though it won't affect the chemicals that are absorbed into the produce.

When buying meat, again if possible, patients should be advised to buy organic to avoid the hormones that are added to the diet of cattle, sheep, pigs and chickens, which make their way into the meat of the animals and thereby into our bodies. It's also important to remember that even if you eat good food, if you eat too much of it, that will not be helpful either.

Principle 3: Eat a Rainbow Diet of Colorful Foods, with Plenty of Fresh Vegetables and Fruit Daily

Eating a healthy diet with a variety of different colored vegetables and fruits helps ensure that the right balance of nutrients, including vitamins and minerals, is consumed. Vegetables, fruits, legumes, nuts and seeds provide a variety of micronutrients and other bioactive compounds, and many have anti-cancer properties. The health benefits of fruits and vegetables are also understood to be partly due to the presence of phytochemicals including carotenoids, sulphoraphanes, flavonoids, salicylates, phytosterols, saponins, glucosinolates, polyphenols, phytoestrogens, lectins and others. Several of these phytochemicals act as antioxidants, preventing damage to cells, protein and DNA [276].

Choose Vegetables and Fruits in Season

When choosing vegetables and fruits, it is generally better to choose those that are in season. According to Chinese medicine diet therapy principles, it is better to eat cooked vegetables and foods in the cold months and not eat raw foods such as salads, which are better eaten in the hotter months. On a practical note, foods in season are generally cheaper and fresher. Fruit is best eaten before the main meal when one is hungriest, as it can help prevent overeating or choosing less healthy options.

Recommended Daily Servings of Fruit and Vegetables

The Australian Dietary Guidelines recommends eating five–six servings of vegetables and two servings of fruit each day for men and (non-breast-feeding) women [17]. Fruit is high in glucose. In general, when eating fruit it is better to eat the whole fruit (as opposed to drinking the juice) as this slows the release of glucose into the blood, thereby helping to reduce spikes in blood glucose levels. Eating the whole fruit also helps satiate the appetite.

Recommended Daily Servings of Vegetables and Fruit

- 5–6 servings of vegetables
- 2 servings of fruit.

Evidence of Protective Effect of Vegetables and Fruits Against Cancer

An early review of 206 human epidemiologic studies and 22 animal studies found consistent evidence for a protective effect of increased vegetable and fruit consumption across a range of cancers including stomach, oesophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon [242]. A study of 61,463 Swedish women found an inverse relationship between total fruit and vegetable consumption and colorectal cancer risk; those who consumed less than 1.5 servings of fruit and vegetables per day had a 65% increased risk of developing colorectal cancer compared with those who consumed more than 2.5 servings [249]. Systematic reviews have found an inverse association between dietary fibre intake and overall cancer risk [53].

Fruit and vegetables are an important source of fibre, as are cereals and grains. The relative contribution towards protection conferred by fruits and vegetables

through the fibre component compared to other constituents is not clear. A systematic review found that a high intake of total daily fibre, and wholegrains and cereal fibre, but not vegetable or fruit fibre, was associated with a decreased risk of colorectal cancer [15]. In another systematic review of breast cancer, again there was a decreased risk of cancer associated with higher overall dietary fibre intake, but not individually for fruit or vegetable fibre (the only one that demonstrated individually a significant inverse association was soluble fibre) [16]. The Nurses' Health Study did not find an association between colorectal cancer risk and fibre intake from fruit or vegetables; however the Health Professionals' Follow-Up Study did find an inverse association between the intake of fruit fibre and distal colon adenomas, but not from cereals or vegetables [206]. Similarly, another systematic review of 14 cohort studies found that those consuming 800 g/day total fruits and vegetables or more had a 26% lower risk of distal (but not proximal) colon cancer compared to those consuming <200 g/day [148]. Dietary fibre is discussed further in Section "Dietary Fibre".

Many of the micronutrients within vegetables and fruits including carotenoids, folate, vitamin C, vitamin D, vitamin E, quercetin, pyridoxine, and selenium have been found, in systematic reviews, to be associated with decreased risk of a range of cancers [276]. The World Cancer Research Fund and American Institute for Cancer Research Second Expert Report concluded that foods containing selenium 'probably protect' against prostate cancer; and there is 'limited evidence' that they are protective against stomach and colorectal cancers. The report states that there is also 'limited evidence' to support that foods containing pyridoxine protect against oesophageal and prostate cancers and that Vitamin E-containing foods protect against oesophageal and prostate cancers [276].

In rural Chinese people, lower blood Vitamin C levels were associated with higher incidence of cancer, in particular cancers of the oesophagus, nasopharynx, breast, stomach, liver, colorectal and lung [42]. Fruit intake was inversely associated with oesophageal cancer and cancer rates were 5–8 times higher in those places where fruit intake was lowest [42]. Stomach cancer has also been found to be significantly higher when blood levels of beta-carotene, plasma levels of selenium and green vegetable intake were lower [147].

Fruits as Sources of Protective Nutrients

Fruits are important sources of protective nutrients (such as Vitamin C plus phenols and flavonoids, beta-carotene and other carotenoid antioxidants), other potentially bioactive phytochemicals, as well as fibre [276]. According to the World Cancer Research Fund and American Institute of Cancer Research Second Expert Report: Food, Nutrition, Physical activity and the Prevention of Cancer: A Global Perspective, foods that are high in Vitamin C probably protect against oesophageal cancer and those containing dietary fibre probably decrease colorectal cancer risk. The report found probable evidence for fruit in reducing risk of cancers of the

mouth, pharynx, larynx, oesophagus, lung and stomach, and suggestive evidence for cancers of nasopharynx, pancreas, liver, and colo-rectum [276].

Vitamin C's role in cancer prevention includes being able to trap free radicals and reactive oxygen molecules (thereby protecting against oxidative damage), regenerating other antioxidant vitamins including Vitamin E, inhibiting formation of carcinogens and protecting DNA against mutagenic attack. Fruits such as apples and grapefruit contain high levels of flavonoids. Flavonoids have antioxidant effects and can also inhibit carcinogen-activating enzymes. Phytochemical antioxidants in fruit can also reduce free-radical damage generated by inflammation [276].

Berries

Berries, particularly strawberries and raspberries, are rich in ellagic acid which has been found, in laboratory studies, to prevent several cancers including bladder, skin, lung, oesophageal and breast. It works via a number of mechanisms including acting as an antioxidant, deactivating specific carcinogens and slowing the reproduction of cancer cells. Strawberries contain flavonoids which act via similar mechanisms. Blueberries contain anthocyanosides which are believed to be the most powerful antioxidants discovered [276]. Black raspberries have been found, in rat studies, to work by inhibiting cell proliferation, suppressing inflammation, blocking angiogenesis and promoting apoptosis [244].

Crucifers

Broccoli and other crucifers are able to arrest cancer cell division, invasion of tissues and angiogenesis, can aid apoptosis, enhance the expression of good genes and block oestrogen [273]. Broccoli has been found to contain glucoraphanin, a glucosinolate precursor of sulforaphane, which has been found to have anti-cancer properties, and 3–4-day-old broccoli sprouts have up to 20 times the amount of this phytochemical compared to the mature plant. Sulforaphane induces carcinogen-detoxifying enzymes, activates apoptosis and blocks cell cycle progression [247], and may target cancer stem cells (responsible for initiating and maintaining cancer, and contributing to drug resistance and recurrence) via several mechanisms including modulation of NF-κB and other pathways [162].

Cooking Hint: Broccoli
How broccoli is cooked is important. Cooking destroys one of its critical enzymes, and therefore it should be lightly steamed only for 3–4 min or stir-fried briefly; boiling for only 5 min reduces the activated nutrient substantially [273].

Table 3.5 Sources of common carotenoids

Sources of both β-carotene and α-carotene	Other sources of α-carotene	Lycopene
Pawpaw, rock melon, mangoes, oranges, carrots, sweet potato, squash and other yellow/orange fruits and vegetables plus some of the green vegetables such as spinach and kale	Peas, green beans, avocado and broccoli	Tomatoes and some other red-colored plants including watermelon, apricot, guava, pink grapefruit and peaches

Based on data from Wilkinson [273], Tanaka et al. [245]

Colorful Veggies

Carotenoids are natural fat-soluble pigments that are responsible for the bright coloration of particular plants and animals. There are several carotenoids in vegetables including α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, zeaxanthin, capsanthin and crocetin. Citrus fruits contain B-cryptoxanthin and marine sources of carotenoids include astaxanthin, β-carotene, zeaxanthin, canthaxanthin, fucoxanthin and lycopene. β-Carotene is the major source of vitamin A as a provitamin A carotenoid [245]. Some sources of common carotenoids are set out in Table 3.5.

Studies have found an association between diets rich in carotenoids and cancer protection. A systematic review of 18 studies (over one million women) found that a carotenoid-rich diet was associated with a lower risk of oestrogen receptor-negative breast cancer (but not oestrogen receptor-positive breast cancer) [289]. Another meta-analysis combining 8 cohort studies found that women with the highest levels of lycopene, β-carotene, and α-carotene had a 22%, 17% and 13% reduced risk of breast cancer respectively compared with women with the lowest levels; risk reduction capacity of carotenoids was greater for oestrogen receptor negative cancers than for oestrogen receptor-positive cancers [82].

In vitro and in vivo studies have demonstrated strong anti-tumor effects of several carotenoids including β-carotene, α-carotene, lycopene, lutein, zeaxanthin, and others [245]. In vitro research has confirmed that synergism between compounds is important. In a study of hormone-dependent prostate cells, combinations of carotenoids or carotenoids and polyphenols and/or other compounds were found to work synergistically to inhibit the androgen receptor activity and activate the Electrophile-Responsive/Antioxidant-Responsive Elements (EpRE/ARE) system. The activation of the EpRE/ARE system was up to four times higher than the sum of the activities of the single ingredients, providing evidence of synergism [165].

Lycopene

Lycopene has a high antioxidant capacity and has been found in some in vitro studies to selectively arrest cell growth and induce apoptosis in cancer cells (without harming normal cells). Lycopene can affect several IGF-1-activated

signalling pathways, PDGF (platelet derived growth factor) and VEGF (vascular endothelial growth factor) signalling pathways, and there is evidence that it has anti-inflammatory actions and can prevent angiogenesis, invasion and metastasis in several cancers [252].

In epidemiological studies, lycopene has been found to be protective against several cancers including prostate, breast, lung, and colon [108]. However, there are other studies that have not found associations. For example, a prospective study of almost 40,000 women found that there was no association between lycopene in diet and plasma lycopene levels and risk of breast cancer in middle-aged and older women [230]. Clinical studies in men with prostate cancer have demonstrated that lycopene supplementation may be a useful adjuvant treatment. A study found that 80% of men who took 30 mg of lycopene/day for 3 weeks prior to radical prostatectomy had smaller tumors than controls, and their PSA levels had decreased by 18% compared to the control group which had increased by 14% [149].

Cooking Hint to Enhance Lycopene Absorption
To enhance the absorption of lycopene, oil or fat is needed—so add some olive oil to cooked tomatoes/tomato paste/tomato sauce to get the full benefit of lycopene from tomatoes.

Garlic

Garlic (Allium sativum) contains at least 33 different organosulfur compounds, plus amino acids, vitamins and micronutrients. The allyl sulphur constituents are understood to be responsible for its health benefits [187] which include positive effects on cardiovascular health and immunity. Recent research indicates that fermented or aged garlic can reduce blood pressure in hypertensive people and has the potential to modulate slightly elevated cholesterol levels [216].

Garlic and risk of cancer

The weight of evidence in the epidemiological literature supports the contention that garlic consumption is associated with reduced colorectal and gastric cancer [226]. Systematic reviews have found that raw or cooked garlic has a protective effect on colorectal cancer [95, 187] and gastric cancer [95, 293]. One of the reviews also found reduced risk for other cancers including prostate, oesophageal, larynx, oral, ovary and renal (but not gastric, breast, lung and endometrial cancers) [95], though a recent one did not find that raw or cooked garlic or garlic supplements lowered colorectal cancer risk [125]. The Iowa Women's Health Study that analysed the diets of almost 42,000 middle aged women found that intake of garlic was inversely associated with risk of colon cancer, as were intakes of all vegetables and dietary fibre [241].

Mechanisms of action of garlic on cancer pathogenesis

How garlic exerts its effect in preventing cancer is not fully elucidated. Whilst it may be ascribed partly to its anti-cancer and protective nutrient/antioxidant effects, it may also be related to garlic's underlying effect on the immune system. Studies on the effect of garlic on the immune system have revealed somewhat conflicting results regarding whether it stimulates pro-inflammatory or anti-inflammatory activity; however, overall the evidence suggests that garlic elicits anti-inflammatory immune responses. There is evidence that garlic can strengthen the immune system within the tumor micro-environment against the immunosuppressive activity of emerging tumors and it has been proposed that garlic is able to act as an immune modulator, shifting the balance from a pro-inflammatory and immunosuppressive environment to an enhanced anti-tumor response [226]. A study of 50 people with inoperable colorectal, liver or pancreatic cancer found that taking aged garlic extract for 6 months improved immune function, significantly increasing number and activity of NK (natural killer) cells [131]. Garlic also acts as a prebiotic, benefiting the gut microbiome.

Animal research indicates that garlic and its allyl sulphur constituents are able to affect colorectal cancer pathways via a variety of mechanisms including induction of apoptosis, DAS inhibition of colorectal cell proliferation, blockage of cell growth, blockage of angiogenesis, inhibition of carcinogen-induced DNA adduct formation, enhancement of carcinogen-metabolising enzymes, inhibition of COX-2 expression, scavenging carcinogen-induced free radicals and inhibition of lipid peroxidation [187]. Other constituents of garlic are also important in its protective effects against cancer including kaempferol, selenium, vitamins A and C, arginine, and fructooligosaccharides [187].

Cooking Hints for Garlic

Heating garlic without peeling inactivates alliinase (which promotes the formation of beneficial sulphur compounds) and substantially decreases or eliminates its active properties. Garlic should be peeled and chopped and allowed to stand for 15–20 min so it can release the enzyme alliinase; then the active agents formed are subsequently not destroyed via normal cooking methods [276].

Mushrooms

Mushrooms have a number of beneficial properties including being immune-boosting, pain-killing, anti-diabetic, anti-viral and antimicrobial, and have anti-cancer properties. They are able to activate the immune system, act as antioxidants, block oestrogen, inhibit invasion and metastasis, stimulate apoptosis, and may prevent recurrences caused by resistant stem cells [199, 273]. Mushrooms

are useful as an adjunct to chemotherapy and radiation therapy as they are able to counter many of the side effects including nausea, bone marrow suppression, anaemia, and lowered resistance [199].

Shiitake mushrooms are common and easy to procure. Shiitake mushroom (*Lentinula edodes*) produces lentinan, a β-glucan which can suppress leukaemia cell proliferation [199]. In vitro and animal studies have found that shiitake extracts have immune-stimulatory [133], anti-proliferative [133], cytotoxic [286], anti-mutagenic [67] and anti-tumor activity [270]. It has also been found to improve immune function in healthy humans [63] and decrease the incidence of chemotherapy-associated side effects in patients with advanced gastrointestinal cancer [191].

Ganoderma lucidum has demonstrated anti-cancer properties, and is used in Chinese herbal medicine. A systematic review of five randomised controlled trials (373 subjects) found that patients incorporating *G. lucidum* in their anti-cancer regime were 1.27 times more likely to respond to chemotherapy or radiation therapy compared to those without. It was found to stimulate immune function by increasing CD3, CD4 and CD8 lymphocyte percentages, and marginally elevate NK cell activity. Those taking *G. lucidum* were also found to have better quality of life after treatment compared with the controls [135].

Principle 4: Limit Red Meat

There is convincing evidence that red meat should have a very limited place within diet and that consumption increases the risk of some cancers. Processed meat should be eliminated from diet as it is carcinogenic. There is no clear data on whether meat from grass-fed animals is better than non-grass-fed animals.

Epidemiological Evidence About Meat

Epidemiological research that has compared diets between countries and death rates from various diseases gives us an insight into patterns in relation to diet that are important. Such studies have demonstrated that increased animal protein consumption is associated with higher rates of heart disease, breast cancer and colorectal cancer [42]. For example, over 40 years ago research indicated that in countries with higher meat, animal protein and sugar consumption and less consumption of cereal grains, rates of colon cancer in women was higher [9]. Similarly, over three decades ago, a study of 142,857 Japanese women over 40, followed for 10 years, found that the risk of breast cancer was 8.5 times higher in women of high socioeconomic class who ate meat daily compared with women of low socioeconomic class who did not [122].

Other research has demonstrated that in countries with higher animal fat (but not plant fat) intake age-adjusted death rates for breast cancer are higher [47]. The

China Study found that higher animal protein intake and animal protein-related blood markers were significantly associated with increased prevalence of cancer in Chinese families [42].

A report from the International Agency for Research on Cancer (IARC) states that eating red meat was found to be associated with an increased risk of colorectal, prostate and pancreatic cancer, and processed meat was found to be associated with stomach cancer [127]. Processed meats include ham, bacon, sausage, hot dogs, corned beef and some delicatessen meats (processing refers to the treatment of the meat to preserve it or enhance the flavour, and includes salting, curing, fermenting, and smoking).

Red Meat and Processed Meat Are Causes of Cancer

A statement that a food causes cancer is much stronger than simply stating there is an association. Published in 2007, the World Cancer Research Fund and American Institute of Cancer Research's Second Expert Report found that red meat is a convincing cause of colorectal cancer, with a substantial amount of evidence from cohort and case–control studies showing a dose–response relationship supported by evidence for plausible mechanisms in humans [276]. It also found 'limited evidence' for red meat as a cause of oesophageal, lung, pancreatic, and endometrial cancers [276]. The report also found 'convincing evidence' that processed meats are a cause of colorectal cancer and 'limited evidence' that processed meats are a cause of stomach, prostate, lung and oesophageal cancer [276].

Classification of Meat as Carcinogenic

Processed meats have now been classified by the International Agency for Research on Cancer (IARC) as 'carcinogenic to humans (Group 1)', and red meat (which includes beef, pork, lamb, goat, mutton, veal, horse) has been classified as a 'probably carcinogenic to humans (Group 2A)' [127]. A systematic review of over 800 studies found that each 50 g portion of processed meat eaten daily increased the risk of colorectal cancer by 18% and each 100 g portion of red meat eaten per day increased the risk by 17% [127].

Potential Mechanisms of Red Meat in Cancer Development

Potential underlying mechanisms for an association between red meat and cancer include generation of potentially carcinogenic N-nitroso compounds by the stomach and gut bacteria. The cooking of some red meats at high temperatures can produce

heterocyclic amines and polycyclic aromatic hydrocarbons which have been linked with cancer. Haem in red meat promotes the formation of N-nitroso compounds and also contains iron, and free iron is one of the most powerful catalysts that can lead to free radical production. In addition, excessive iron can induce hypoxia signalling, and activate oxidative transcription factors and pro-inflammatory cytokines [276].

It is known that oestrogen levels are a critical determinant of the risk of breast cancer [281]. Campbell and Campbell argue that higher dietary fat is associated with higher blood cholesterol and these, in addition to higher female hormone levels, are associated with earlier age of menarche and increased breast cancer [42]. They argue that a diet rich in animal-based foods will maintain high levels of these hormones, thereby increasing the lifetime exposure to female hormones (which is associated with increased risk of breast cancer).

IGF-I normally manages the rate at which cells grow and are discarded. However, under unhealthy conditions it becomes more active, stimulating the birth and development of new cells and inhibiting the removal of old cells, stimulating cancer development. Men who eat meat have significantly higher levels of IGF-I compared with vegans [4]. Men with higher than normal blood levels of IGF-1 have 5.1 times the risk of advanced stage prostate cancer [50].

In addition, sulphur-containing amino acids from animal protein lower blood pH which suppresses production of 1,25(OH)2 vitamin D [1,25(OH)2D], the biologically active form of vitamin D [107]. Vitamin D deficiency has been implicated as a risk factor in various cancers, including prostate cancer [107], though one case–control study found that both low and high levels of 25(OH)vitamin D_3 were associated with prostate cancer [256]. Vitamin D is discussed in Chap. 4.

Principle 5: Incorporate Healthy Dairy Products

Approximately 64% of the total calories from whole cow's milk are from fat [42]. Thus, diets high in dairy foods may contribute substantially to the overall amount of fats in the diet. This may be relevant if a person is overweight or obese. In relation to whether dairy foods might be associated with cancer, the evidence is mixed.

Animal Research

Studies in rats have found that increased intakes of casein, a protein in milk, was associated with promotion of development of mammary cancer, operating through a network of reactions, and also via the same female hormone system that operates in humans. Rat and mice studies also showed that diets high in casein promote liver cancer [42].

Link Between Dairy and Prostate Cancer

The World Cancer Research Fund and American Institute for Cancer Research Second Expert Report found that diets high in calcium are a probable cause of prostate cancer, and there is 'limited evidence' that high milk and dairy consumption can cause prostate cancer. There is 'limited evidence' that cheese consumption is associated with colorectal cancer [276].

Systematic reviews have also found evidence of an association between dairy products and prostate cancer [276]. One review found that men with the highest dairy consumption had approximately twice the risk of prostate cancer, and four times the risk of metastatic or fatal prostate cancer compared with those consuming low amounts [49]. The potential mechanisms underlying the association with dairy and prostate cancer may include IGF-I which increases with intake of animal-based foods such as meat and dairy. In addition, milk and other dairy foods have animal protein and large amounts of calcium which can suppress the production of 1,25 Vitamin D (which plays a role in prevention of cancer) [42].

Colorectal Cancer and Dairy

The World Cancer Research Fund and American Institute for Cancer Research Second Expert Report found 'limited evidence' that cheese consumption is associated with colorectal cancer and that milk 'probably protects against colorectal cancer' (it also found there is 'limited evidence' that it protects against bladder cancer) [276].

Breast Cancer and Dairy Foods

An earlier meta-analysis did not find an association between intake of dairy foods and breast cancer [177]. A more recent meta-analysis found that dairy consumption was inversely associated with risk of developing breast cancer and that the type of dairy was important—subgroup analysis demonstrated that yoghurt and low-fat dairy significantly reduced the risk, whilst other sources of dairy did not [287].

Benefits Associated with Different Types of Milk

Cows eliminate toxic substances via fat. Therefore, one might postulate benefits of low-fat milk. Organic milk will not have associated toxicity derived from pesticides and other chemicals used to spray grass and foods that the cows feed on. Also, there

is increasing evidence of an association between A1 beta-casein, a protein produced by the majority of cows of European origin, and milk intolerance. Digestion of bovine A1 beta-casein but not A2 beta-casein has been found to lead to activation of μ-opioid receptors in the gastrointestinal tract and body and rodent studies have shown that it significantly increases an inflammatory marker myeloperoxidase [197].

Good Sources of Dairy

There are good sources of dairy including natural yoghurt and kefir which contains a range of probiotics that are beneficial to the gut microbiome. Thus, it is useful to incorporate some of the good sources of dairy like yoghurt and kefir, in particular in patients who have been given antibiotics. Most of the commercial yoghurts and other fermented dairy products are heated to sterilise them. Hence, it is important to select a non-sterilised product to obtain maximum benefit. Probiotics will be discussed in detail under **Principle 12**: Eat For Your Gut Microbiome.

Principle 6: Reduce Overall Consumption of (Unhealthy) Fats

This section will discuss overall fat intake in diet, whilst the section following this will hone in on different kinds of fats and oils.

Expert Panel Findings on Fat Intake and Cancer

The World Cancer Research Fund and American Institute of Cancer Research Second Expert Report found that there is 'limited evidence' that total fat intake is a cause of postmenopausal breast cancer, and that total fat intake and butter consumption (separately) are causes of lung cancer (though it stressed that the main cause of lung cancer is still tobacco). They also found there was a limited amount of fairly consistent evidence that animal fat consumption is a cause of colorectal cancer [276].

Population Studies of Fat Consumption and Interventions of Lowered Fat Intake

Epidemiological research indicates that high fat intake is associated with several chronic diseases including cancer. Countries with a higher intake of fat, in particular

animal fats, have a higher rates of breast cancer [42, 46, 110, 220, 260]. Nearly 30 years ago, the 1988 Surgeon General's Report on Nutrition and Health stated that comparisons between populations indicated death rates for cancers of the breast, prostate and colon were directly proportional to estimated dietary fat intakes [260].

However, there have been some conflicting findings in several large intervention studies, with some suggesting that lowering fat intake is associated with decreased breast cancer risk [52] and others suggesting it isn't [59, 104, 208]. The Women's Intervention Nutrition (WIN) Study in 2437 women with breast cancer found that after 60 months, those in the low-fat diet had a significantly lower disease recurrence (9.8%) than those in the control group (12.4% women) corresponding to a 24% reduced risk [52]. The Women's Health Initiative Study found a non-significant reduction (9%) in breast cancer incidence associated with a low-fat diet in postmenopausal women over 8 years follow-up (it just failed to reach statistical significance thus the result still may be due to chance) [208] and no significant reduction in risk of invasive colorectal cancer [28]. Research has also found that when overweight/obese postmenopausal women were placed on a very low-fat, high-fibre diet for 2 weeks, there was a significant reduction in serum insulin and IGF-1, and in vitro growth of breast cancer several cell lines was reduced and apoptosis increased [22]. A low-fat, high-fibre diet was associated with lower serum bioavailable estradiol concentration in women diagnosed with breast cancer [219]. These studies suggest that low-fat/high-fibre diets, at the level of physiology might play a positive role.

Problems with Research Methodology

Contrary to findings of others, there have been other studies in women with breast cancer including the large Nurses' Health Study that did not find any association between lowering fat intake and breast cancer [59]. This study has been criticised by Campbell and Campbell [42] who explain that in this study population, there was a very *low* correlation between animal protein and total fat intake (being a typical American diet), and whilst there was variation within the cohort of percentage of calories from fat in their diet, the nurses nearly all ate a diet that was rich in animal foods. Thus, they explain, the Nurses' Study cohort was not adopting the diets shown in the China Study or other international studies to be associated with low breast cancer rates [42], that is diets low in animal-based foods. In the China Study and other international correlation studies, the correlation between fat intake and animal protein intake has been high. The China Study of rural Chinese found that when dietary fat was reduced from 24% to 6%, risk of breast cancer was lowered. However, the authors argued that this might be a reflection of an association between animal-based foods and breast cancer [42].

There's another point to be made about the study methodology involved population studies—unless they look at the types of fats involved, it's difficult to make

a comment about the impact of low- or high-fat diets—some fats are very good for the body, others are not. A high fish fat diet, for example, has been found to reduce colorectal cancer recurrence [239]. Avocado is another food that contains beneficial fats. Even if a diet was low in fat, if these were bad fats, then conceivably it might not confer any protection against breast cancer or other cancers. Not all oils and fats are created equal.

Principle 7: Consume Healthy Fats and Oils and Avoid Unhealthy Ones

Fats and oils are the most energy-dense components of diets. Dietary fats sources include animal products, including meat, milk and other dairy foods, as well as plants, including nuts and seeds. Meat, milk and dairy are the major sources of fat in most high-income countries [276]. A number of oils and fats are beneficial for the body, whilst some have been linked with disease. High levels of trans-fatty acids have also been associated with coronary heart disease [276] and raised levels of CRP [167], a marker of inflammation, and because of this should definitely be avoided.

Dietary fat is mostly made up of triglycerides, three fatty acid molecules attached to a glycerol backbone. These fatty acids are either 'saturated' or 'unsaturated'. Unsaturated fats are typically divided into monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). For further information see Table 3.6.

Table 3.6 Unsaturated and saturated fats

• Unsaturated fatty acids may be monounsaturated (they have one double bond) or polyunsaturated (≥ 2 double bonds)
• Where the first double bond is located along the carbon chain is denoted by an 'n'. Linoleic acid is '$n-6$' (also known as Omega-6 fatty acids) and alpha-linolenic acid is '$n-3$' (also known as Omega-3 fatty acids)
• Saturated fats tend to be solid at room temperature whilst unsaturated fats are liquids i.e. oils
• When unsaturated fatty acids in oils and marine sources undergo partial hydrogenation, they are transformed into trans-fatty acids whilst if they undergo complete hydrogenation, they are transformed into saturated fatty acids
• Conversion into saturated fatty acids extends the shelf life of the unsaturated oils that would, under normal conditions, potentially go rancid
• Trans-fatty acids have been linked with cardiovascular disease; however, the effect on cancer is unknown [276]

Omega 3 and Omega 6 PUFAs

Polyunsaturated fatty acids (PUFAs) include Omega 3 ($n-3$ PUFAs), Omega 6 ($n-6$ PUFAs) and Omega 9 ($n-9$ PUFAs). There are both short-chain forms of $n-3$ PUFAs (alpha-linolenic acid, the only Omega 3 source found in plants) and long chain forms (eicosapentaenoic acid, EPA and docosahexanoic acid, DHA). The best sources of $n-3$ PUFAs are fish oils about which quite a lot is known. The Japanese have a diet that is high in fish that contain healthy $n-3$ PUFAs and this contributes to them having one of the highest life expectancies.

Omega 6 is divided into a short-chain form, linoleic acid, which is the most prevalent PUFA in western diets, and the longer chain form, arachidonic acid (AA). Both $n-3$ and $n-6$ PUFAs are essential fatty acids that need to be taken into our bodies via diet.

n − 3 PUFAs and reduced risk of cancer

The $n-3$ PUFAs are particularly important as they have been shown to decrease risk of particular cancers including breast, prostate, colorectal cancer and adenocarcinoma [74, 89, 145, 259]. The EPIC study, a prospective study of 478,000 men and women in Europe, found that fish intake was inversely associated with risk of colorectal cancer [189], and laboratory studies have found these can reduce the progression of colorectal cancer [259]. Another study found that intake of EPA was associated with decreased risk of ER + PR + breast cancer [145] and that n-6 PUFA intake was positively associated with development of ER+ PR+ tumors (which are the majority of breast cancers) [145]. Omega-3 fatty acids are likely to exert anti-cancer effects by impacting several different pathways associated with cancer pathogenesis including cell proliferation, cell survival (including promoting apoptosis), angiogenesis, inflammation, metastasis and epigenetic abnormalities [136].

The importance of the ratio of n − 6 to n − 3 PUFAs

The $n-6$ PUFAs also play an important role in the body; however, the problem is that they are also pro-inflammatory. The ratio of $n-6$ PUFAs to $n-3$ PUFAs is very important: high levels of $n-6$ PUFAs or a high $n-6$ to $n-3$ PUFA ratio promotes inflammatory conditions and diseases such as cancer and cardiovascular disease, whereas increased levels of $n-3$ PUFAs or a low $n-6$: $n-3$ PUFA ratio is suppressive for such conditions [235]. The ratio of $n-6$ to $n-3$ PUFAs 3 in western diets is somewhere between 10:1 and 25:1 [273, 235, 236], whereas several sources suggest that humans evolved on a diet where the ratio of these two fatty acids was closer to 1:1 [235]. This may be due to the move away from animal fats towards polyunsaturated vegetable oils and margarines [214, 273]. Western diets are therefore excessive in the amount of $n-6$ and deficient in $n-3$ PUFAs. Recent research has demonstrated benefits of lowering the $n-6$ to $n-3$ PUFA ratio which was found to be associated with decreased risk of COX-dependent adenocarcinoma [74]. Sources of $n-3$ and $n-6$ PUFAs are set out in Table 3.7.

For further information about $n-3$ and $n-6$ PUFAs, refer to the Additional Reading section of this chapter.

Table 3.7 Examples of sources of $n-3$ and $n-6$ PUFAs

Short-chain $n-3$ (alpha-linolenic acid) sources	Long chain $n-3$ (EPA, DHA) sources	$n-6$ linoleic acid sources	$n-6$ arachidonic acid sources
Flaxseed oil, walnuts (black, English and Persian), chia seeds, dried butternuts, beechnuts, green and raw soybeans, dry soybeans (lesser amount than the green, raw ones), oats/germ, other nuts (hickory, almond, pecans, mixed nuts)	EPA: Fish, fish oils, marine sources DHA: Fish, fish oils, specialty egg/dairy products Fish sources containing DHA plus EPA include: Atlantic salmon, raw European anchovy, Atlantic herring, mackerel, trout	Vegetable oils: corn, sunflower, safflower, soybean, canola, peanuts Animal meats	Animal sources only: liver, egg yolks, animal meats and seafood

Based on data from Mercola [174], Wilkinson [273], DHA/EPA Omega 3 Institute [73]

Patient Advice
On a more practical note it is far too difficult for the patient to try to work out ratios of $n-3$: $n-6$ oils. It's far easier simply to advise them to emphasise the sources of Omega 3 fatty acids such as fatty fish (salmon and others), which can be added to their diet.

Flaxseeds and Lignans

Flaxseeds are a good source of $n-3$ PUFAs; however, there is a difference between flaxseeds and flaxseed oil (as there is between sunflower seeds and sunflower oil). The oil is highly unstable whereas the seeds are not. Importantly, as well as being a good source of $n-3$ PUFAs, specifically alpha-linolenic acid, flaxseeds also contain important lignans which have anti-cancer properties [273].

Lignans are compounds found in most fibre-rich plants including grains (wheat, barley, and oats), legumes (e.g. beans, lentils, and soybeans), vegetables (e.g. garlic, asparagus, broccoli, carrots, soybean), seeds (sesame, pumpkin) and some berries [251]. The major lignan in flaxseed is called secoisolariciresinol diglucoside (SDG) which is converted in the large intestine to active mammalian lignans, enterodiol, and entero-lactone. There is evidence that these active lignans are able to reduce the growth of tumors, in particular those that are hormone-sensitive (breast, endometrium, and prostate) and skin cancer [251].

Hint: Fish Versus Flaxseeds as Sources of $n-3$ PUFAs
Flaxseed mostly contains alpha-linolenic acid (ALA), and the body needs to convert this to the essential fatty acids, EPA and DHA. However, it is estimated that only 5–10% of ALA is converted to EPA and only 2–5% if converted to DHA. In contrast, fish such as salmon and krill are direct sources of EPA and DHA. Fish also contain a lot of other beneficial nutrients including protein, iodine, selenium, vitamin D and other vitamins and minerals depending on the species of fish [112]. Thus, in terms of sources of DHA and EPA, it is best to consume fish about which we know quite a lot.

Olive Oil

Olive oil is a key feature of the Mediterranean Diet which has been found to be associated with lower risk of cardiovascular disease and cancer, as discussed at the beginning of this chapter. Epidemiological studies have found that consumption of virgin olive oil is associated with reduced cardiovascular disease [221], and atherosclerosis [146]. A systematic review found that olive oil intake was associated with reduced risk of cancers of the upper digestive and respiratory tracts and breast cancer, and possibly colorectal cancer [201].

The major phenolic compounds including simple phenols (hydroxytyrosol, tyrosol), secoiridoids (oleuropein) and lignans in olive oil have antioxidant capacity, and are able to scavenge free radicals and protect against peroxidation [196]. Experiments in mice have shown that Extra Virgin Olive oil has strong analgesic, anti-inflammatory effects, and anti-cancer effects, inhibiting the growth of colon tumors [94]. Rat studies have also found that dietary olive oil may prevent colon carcinogenesis, the effects which partly may be via modulation of arachidonic acid metabolism and local PGE2 synthesis [23].

It is of interest that the olive tree can survive up to 2000 years, and it is thought that this is due to the protective chemicals that the trees can produce. It would appear that some of these protective chemicals may also protect humans who consume the olives and other components of the plant.

Coconuts and Coconut Oil

In the past, because coconut oil contains saturated fat it has been denigrated along with other saturated fats. However, in more recent times there has been an increased interest in the protective capabilities of coconut. The various parts of the coconut, including the coconut kernel and water and oil, have a range of medicinal properties

including anti-bacterial, anti-fungal, anti-viral, anti-parasitic, antioxidant, hypoglycemic, anti-atherogenic, anti-thrombotic and immunostimulatory effects [65].

Canola Oil and Other Vegetable Oils

In general, vegetable oils should be avoided in favour of healthier oils including olive oils, avocado oils and coconut oil. The higher use of vegetable oils such as sunflower oils and spreads which are rich in $n-6$ PUFAs has dramatically shifted the ratio of $n-6$ PUFAs to $n-3$ PUFAs [234]. This has shifted the balance of eicosanoids synthesised from DHA and EPA (produced from $n-3$ PUFAs) to favour eicosanoids derived from arachidonic acid (synthesised from $n-6$ PUFAs); arachidonic acid leads to the production of leukotrienes, prostaglandins and thromboxanes, including platelet activating factor (PAF). [214]. This imbalance leads to a pro-inflammatory state.

Canola oil is produced from the rapeseed plant. Rapeseed oil is a monounsaturated oil with a high erucic acid content, a fatty acid associated with Heshan's Disease which causes fibrotic lesions in the heart. A large amount of canola oil is now genetically modified, and the process used to modify the rapeseed plant produces canola oil with less erucic acid and more oleic acid. The safety of long-term ingestion of the small quantities of erucic acid in canola oil has not been established. In addition, it undergoes a deodorization process that turns Omega-3's into trans-fatty acids. Consequently, there have been concerns about increased cancer risks due to the hydrogenation process, blood platelet abnormalities, free-radical damage and retardation of normal growth (it is illegal to use in infant formulas) [79].

In general, oils from trees appear to be protective whereas oils from other types of plants do not.

Nuts

Nuts have been found to confer health benefits, discussed earlier. A 2013 study found that a handful of mixed nuts each day will increase longevity by 20% [20]. A study of over 34,192 Seventh Day Adventists found that those who ate nuts ≥ 5 times/week had a significantly (50% less) reduced risk of fatal and non-fatal ischaemic heart disease compared to those who ate nuts <1 time/week [102]. Most nuts contain mostly Omega-6 fatty acids so they should be balanced with Omega-3 oils [273]. Remember, Omega-6 fatty acids are necessary in the diet, it's the ratio to Omega-3's that needs to be right.

Take Home Messages About Fats

Take Home Messages About Fats

1. Limit intake of foods high in saturated fat (some of which often also contain refined sugar) such as many biscuits, cakes, pastries, pies, processed meats, commercial burgers, pizza, fried foods, potato chips, crisps and other savoury snacks
2. Good oils to add to diet include olive oil, avocado, coconut
3. Avoid fried foods, canola oil and other vegetable oils including safflower and sunflower
4. Evidence suggests that fish fats are the most protective
5. Remember to add oils before serving vegetables (so that you are getting some good oils that have not been altered by heat)
6. Add a handful of nuts to diet daily—include walnuts which contain Omega-3 fatty acids and brazil nuts which contain selenium
7. Cook with oils that have a high smoke point and are healthy, e.g. olive oil, coconut oil, sesame oil, grape seed oil, rice bran oil or macadamia nut oil.

Principle 8: Keep Hydrated But Choose Your Drinks Wisely

In this section, we will look at some popular beverages, including coffee, green and black tea, water, soy and alcohol. But first, a quick note about the temperature of drinks and what the current evidence indicates.

Some Like It Hot (But It May Not Be Good for You)

The 2016 International Agency for Research on Cancer (IARC) review of coffee, mate and very hot beverages concluded that there is 'limited evidence' in humans for the carcinogenicity of drinking very hot beverages in relation to oesophageal cancer [166]. This conclusion was based on studies of drinking mate (South American drink), tea and other very hot beverages. Another study similarly found an association between increased temperature and increased risk of oesophageal cancer [132]. Thus, it would be prudent to advise patients to drink their beverages at slightly lower temperatures and avoid hot or very hot temperatures.

Coffee

Over recent years, there is increasing evidence that coffee may be beneficial for health and that it is not a risk for cancer that it was once thought it could be. In fact, it may even be protective against some cancers. Drinking coffee enhances social communication, giving it a very important added benefit in terms of health.

Classification in relation to potential carcinogenicity

There have been over 500 epidemiologic studies in Japan, Europe and America investigating whether there is an association between coffee drinking and risk of developing a range of cancers [57]. The International Agency for Research on Cancer (IARC) reviewed the scientific evidence in relation to coffee and carcinogenicity. In its previous review in 1991, the IARC classified coffee as 'possibly carcinogenic to humans (Group 2B)'. That classification has now changed—it has been classified as 'unclassifiable as to its carcinogenicity to humans (Group 3)' [166]. The 2016 IARC review of the literature found no consistent association between coffee consumption and bladder cancer, and no association with pancreas or prostate cancer. Either no association or a modest inverse association was found between coffee consumption and female breast cancer, and there was evidence of an inverse relationship for liver and endometrial cancers. The evidence in relation to a range of other cancers, however, was found to be inadequate.

> '*Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day for a 70-kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women (see below). No health concerns in relation to acute toxicity, bone status, cardiovascular health, cancer risk or male fertility have been raised by other bodies in previous assessments for this level of habitual caffeine consumption and no new data have become available on these or other clinical outcomes which could justify modifying these conclusions*' **European Food Safety Authority 2015** ([84], p. 74).

Evidence of a protective effect of coffee against cancer

When looking at individual studies, there is evidence that coffee may be protective against particular cancers. Research has found that coffee consumption is associated with a reduced risk of a range of cancers including the following:

- colorectal [105, 160, 228]
- pancreatic [76, 284]
- liver cancer [19, 37, 224], as well progression to liver cancer in Hepatitis B carriers [159] and progression of liver cancer in those with Hepatitis C [99]
- oral cavity and pharynx [257, 284, 290]
- glioma [176]
- oesophageal [284, 291].

Coffee and breast cancer

The research conclusions are mixed for breast cancer [57]. In women with BRCA1 and BRCA2 mutations, it seems that coffee may be protective against breast cancer [188]. In postmenopausal women, coffee consumption has been found in several studies to reduce risk of breast cancer also [246, 161]. However, a recent meta-analysis found no significant association between coffee consumption and reduced risk of breast cancer except in the case of oestrogen receptor-negative women where an inverse relationship was found [163] and another meta-analysis analysis found a weak relationship between coffee consumption and increased risk [134]. For stomach, lung cancer and bladder cancer, the research is inconclusive. A detailed summary of research on coffee and its effects on health can be found at the Institute for Scientific Information on Coffee [57].

Coffee and co-morbidities

Since cancer sufferers often have or can develop co-morbidities, it is worth noting that there is also some evidence that coffee is protective against diabetes [261] and can confer neuroprotection in Parkinson's Disease [207].

Tea

Tea has been found to have many positive health benefits including lowering cholesterol, and preventing age-related memory loss and has anti-cancer and anti-inflammatory properties.

There are several compounds in tea including polyphenols, alkaloids (caffeine, theophylline, theobromine), chlorophyll, amino acids, carbohydrates, proteins, fluoride, aluminium, minerals, volatile organic compounds and trace elements. The health benefits of tea are thought to be due to the polyphenols, which include the catechins. The most abundant catechin in green tea is epigallocatechin-3-gallate (EGCG); others include Epigallocatechin (EGC), Epicatechin-3-gallate (ECG) and Epicatechin (EC). Black tea also has these catechins; however, the concentrations of these are much lower than in green tea [183].

Anti-cancer properties of tea

There is evidence from animal studies and epidemiologic studies of humans that suggest that tea may have anti-cancer properties. Animal studies have demonstrated that tea and its constituents are able to inhibit cancers of the skin, lung, oral cavity, oesophagus, liver, stomach, prostate and others [155]. Results of over 50 epidemiologic studies of the association between tea consumption and risk of cancer published since 2006 have been variable; however, some have found an association between tea intake and reduced risk of cancers of the colon, breast, ovary, prostate and lung. Inconsistency of research results may be due to lifestyle factors, smoking, alcohol consumption, tea preparation methods and others [183]. Two randomised

controlled trials have found green tea consumption was associated with a decrease in a marker of oxidative DNA damage that may be a predictor for increased cancer risk [111, 168].

Mechanisms of action of tea

The exact mechanisms by which green tea may help prevent cancer have not been established. However, the main polyphenols in green tea and the theaflavins and thearubigins in black teas are protective plant chemicals and may protect cells against DNA damage [117]. Tea polyphenols can inhibit tumor formation and induce apoptosis [155], and tea catechins can inhibit angiogenesis and tumor cell invasiveness [288]. Other mechanisms of action of green and black tea include anti-mutagenic, anti-proliferative and anti-neoplastic activity. For more information about green and black tea, see the Additional Reading section at the end of the chapter.

Key Point

- Green tea has more protective chemicals and in higher amounts than black tea and is therefore more protective; however, black tea still has some beneficial actions.

Soy

Soy is widely consumed in Asia in a variety of forms, including tofu, dried or green or fermented soybeans, miso (fermented soy bean paste), soy milk and others. There is some controversy in the literature about whether soy is good or bad for health, particularly in western countries. There seems to be a fear that soy, being a phytoestrogen, is somehow dangerous to women with oestrogen-receptive-positive cancers. However, these phytochemicals are often significantly altered (into many different metabolites) by the gut flora. Much more research into the potential benefits (or otherwise) of these metabolites is necessary before any definitive statements can be made.

Asian women have a lower rate of breast cancer than in western countries [6]. Higher intake of soy during childhood and adulthood in Asian-American women was found to be associated with a reduced risk of breast cancer [280]. A meta-analysis found that in Asians, risk of breast cancer decreased with increasing intake of soy, whilst in the relatively low soy-consuming Western populations, soy intake was unrelated to breast cancer risk [282]. Another meta-analysis of 18 epidemiologic studies from 1978 to 2004 that examined soy exposure and breast cancer risk found that when the results of all women were considered, high soy intake was modestly associated with a reduced risk of breast cancer (OR 0.86, 14% reduction) but there was no significant association when only women from Asian countries were analysed [255]. This may have been due to the low baseline of breast cancer in Asia to begin with.

Soy contains isoflavones, phytoestrogens that are thought to reduce risk of breast cancer, with Genistein, Daidzein and their glucosides being the main ones. Several in vitro studies and animal studies have demonstrated that soy or isoflavones have anti-cancer effects on hormone-related cancers, and there may be several mechanisms involved including oestrogenic and anti-oestrogenic activities [195, 175].

Water

The recommended intake of water is 6–8 glasses per day; however, this can vary depending on illness, exercise, spending time in the heat and other factors. A good rule of thumb is to sip water or healthy, low-caffeinated green or herbal teas during the day and listen to your body to regulate intake and adjust when needed. Clinicians can advise patients to check the color of their urine as an indicator of hydration—darker urine can indicate the need for better hydration.

Much of the water supply in countries like Australia and the US has additives such as chlorine, fluoride and, other contaminants such as trihalomethanes. Serious contaminants can also make their way into drinking water, including chemicals used to spray crops, industrial pollutants and chemicals leached out of plastic pipes used to carry water.

Coal-fired power plants are problematic. Relatively large amounts of particulate and oxidised mercury are released from these power plants and they are rapidly deposited locally [222]. Bodies of water nearby are expected to receive greater atmospheric deposition of mercury than those further away [141, 222]. One study found that contrary to what would be expected, the mercury level in fish closer to coal power plants was lower than fish in lakes further away [222]. However, this finding was found to be associated with selenium—levels of selenium were found to be much higher in lakes closer to coal power plants, and selenium antagonizes mercury. The study also concluded that water quality characteristics such as pH, sulphate, and DOC all play important roles in mercury accumulation in water systems and fish tissue [222].

Fluoride in water

There is evidence that contaminants in water including fluoride may be toxic to the body and associated with a range of diseases including cancer [158]. This is, of course very controversial, but with such large vested interests involved, this would hardly be surprising.

Biochemist Dr. John Yiamouyiannis spent several years researching the toxicity of fluoride and found that fluoride is cumulative, and that it damages the immune system, poisons more than 100 enzymes, increases risk of cancer, and increases the risk of autoimmune diseases, amongst other things [158]. Dr. Dean Burke, former head of the Cytochemistry Section of the U.S. National Cancer Institute and Dr. John Yiamouyiannis created quite a stir in the 1970s when they testified before the US Congress that there was a greater rate of cancer in ten fluoridated US cities compared with ten non-fluoridated ones [283].

Epidemiological studies have suggested an association between fluoridation of water and osteosarcoma as far back as 1955 [61], including a matched case–control study in young boys that found exposure to fluoride in their 6th to 8th years was associated with a five to sevenfold increase in risk of contracting osteosarcoma by age twenty [25]. Studies in male rats have also demonstrated a significant dose-related increase in risk of osteosarcoma [185]. The vast majority of western European countries do not fluoridate their water [97].

Chlorine in water

Fluoride is not the only villain: exposure to chlorine in water (chlorination disinfection by-products), including from bathing and swimming, has also been linked to bladder cancer [172, 266, 124] and possibly other cancers including brain [44] and colorectal cancer [81], and other chemicals including arsenic have also been implicated in several cancers also [170].

Water filters

Where possible, it is advisable that water is filtered to remove as many impurities as possible, and alkalinise the water. Filtered water also tastes better. Reverse osmosis filters are able to remove the majority of fluoride in town water, and there are a variety of options including whole house water filtration systems, smaller units that filter via the water taps, and benchtop units. Of course, the cost varies considerably. Bottled water, whilst handy when travelling, may not be a great environmental choice if used on a daily basis. Australians are particularly high consumers of bottled water, which is curious given their relatively clean water supply. However, this may not be so much about health concerns as savvy marketing.

Alcohol

There is some controversy about whether consuming alcohol can confer benefits or the opposite for health. For years it was believed that moderate consumption of alcohol had a cardio-protective effect. In more recent times, however, it has been found that there is convincing evidence that alcohol can cause cancer of the oropharynx, larynx, oesophagus, liver, colon, rectum and breast [62, 276] and probably also pancreatic cancer [258]. It is estimated that worldwide, alcohol-attributable cancers at these sites constitute 5.8% of all cancer-related deaths [62]. There is also growing evidence to implicate alcohol in development of skin, prostate and pancreatic cancer [116, 231, 223]. The risk of cancer has been found to increase with increasing alcohol consumption on a regular basis.

For women, increased alcohol consumption has found to be (statistically) significantly associated with increased risk of cancer of the oropharynx (increased risk per 10 g/day of 29%), oesophagus (22%), larynx (44%), rectum (10%), liver (24%), breast (12%) and total cancer (6%). The trends were similar for those who only drank wine compared to those who drank other types of alcohol [5].

Some of the evidence in relation to the association between alcohol and cancer risk is set out in Table 3.8.

Table 3.8 Evidence of association between cancer and alcohol

Colorectal cancer
• A meta-analysis of 61 studies found that consuming more than one drink per day is associated with increased colorectal cancer risk; risk increased with amount of alcohol consumed daily [91] • A meta-analysis found a J-shaped relationship between alcohol consumption and colorectal cancer, providing evidence for a statistically significant association with heavy ($\geq$50 g/day), though not light or moderate, alcohol drinking and colorectal cancer mortality [39] • A meta-analysis of 57 studies found that people who regularly drank around 3.5 drinks daily had 1.5 times the risk of developing colorectal cancer compared to occasional drinkers or non-drinkers [91]
Breast cancer
• A meta-analysis of 53 studies found that women who drank more than 45 g alcohol/day had almost 1.5 times the risk of developing breast cancer compared to non-drinkers (Relative Risk 1.46), and in those who consumed 35–44 g alcohol/day, there was a 32% increased risk of breast cancer (Relative Risk 1.32). For every 10 g alcohol consumed per day, there was a 7% increase in risk of breast cancer [113] • Other meta-analysis studies have supported the contention that alcohol consumption is associated with increased breast cancer risk [142] • The Collaborative Breast Cancer Study, a population-based study found that moderate alcohol intake before breast cancer diagnosis was associated with lower overall breast cancer mortality (3–6 drinks/week vs non-drinkers: HR 0.85); however, they found no association with alcohol intake after diagnosis [186] • A prospective Danish cohort study found an increased risk of recurrence with higher alcohol consumption (>2 units/day vs. $\leq$1 unit/day: HR 1.65) but also found that average alcohol intake was greater after breast cancer diagnosis compared to before [123] • The After Breast Cancer Pooling Project which is the largest and longest study so far to assess recurrence found that overall increased levels of alcohol were not associated with recurrence or overall survival, but there was an increased risk of recurrence in postmenopausal women who regularly consumed alcohol ($\geq$6.0 g/day) (HR, 1.19; 95% CI, 1.01–1.40) [152]
Head and neck cancer
The NIH-AARP Diet and Health Study found mixed results in relation to the association between alcohol consumption and risk of head and neck cancer: • There was evidence of a dose–response relationship between alcohol consumption and risk of head and neck cancer: women and men who consumed >3 drinks per day has 2.5 and 1.5 times the risk of cancer (Hazard Ratios 2.5 and 1.48 respectively) • Consumption of up to one standard alcoholic drink per day was associated with lower risk of head/neck cancer compared to non-drinkers [100]

Mechanisms of action

The mechanisms by which alcohol may contribute to cancer include the following:

- Metabolism of ethanol in alcohol produces acetaldehyde which is a carcinogen that can damage cellular DNA and proteins. The International Agency for Research on Cancer (IARC) has listed acetaldehyde as a Group 1 Carcinogen. The metabolism of acetaldehyde on the other hand produces acetic acid, an extremely important communications molecule for the immune system.
- Generates reactive oxygen species which damage DNA, proteins and fats.

- Impairs body's ability to absorb nutrients which are associated with increased risk of cancer (e.g. Vitamins A, C, E, folate, carotenoids).
- Raises oestrogen levels (which are implicated in higher risk of breast cancer) [171].
- Ethanol is hypothesised to play a role in breast cancer development by down-regulating the tumor suppressor gene BRAC1, causing increased transcriptional activity of ERα (key oestrogen receptor) which then leads to increased cell proliferation and increased chance of genetic damage [171].

Some evidence of benefits of wine

There is research that suggests some benefits associated with one of the components of red wine, resveratrol (Malbec and Pinot Noir varieties contain the most). Laboratory research indicates that resveratrol has several anti-cancer properties including being anti-inflammatory, antioxidant, an immune system modulator, being able to block cancer cell proliferation and being able to sensitise cancer cells to chemotherapy [273]. It also has antibiotic and anti-fungal properties [273].

Key Point
Resveratrol can be obtained by eating fruits that contain it such as raspberries and red grapes, or by taking a resveratrol supplement, rather than drinking alcohol.

A recent study in female patients with non-Hodgkinson's lymphoma found that pre-diagnostic wine consumption reduced the risk of death and relapse in women. The study found that women who drank wine had better overall survival than women who had never drunk wine. In those with diffuse large B cell lymphoma (DLBCL), those who consumed wine for more than 25 years had a significantly reduced risk of death and risk of relapse, secondary cancer or death (64 and 62% reduction respectively). However, DLBCL patients who started drinking liquor before the age of 21 had a significantly increased risk of death and increased risk of relapse, secondary cancer or death compared to those who were 'never drinkers' [114].

Recommendations on alcohol consumption in relation to cancer

The general advice given in dietary guidelines, such as recommendations from the World Cancer Research Fund and American Institute for Cancer Research Second Expert Report is that, based on evidence in association with cancer, no alcohol should be consumed [276]. However, this report also stated that on the basis that there is some evidence of a cardio-protective effect, if alcohol is to be consumed, men should limit their consumption to no more than two drinks per day and women should limit theirs to one drink per day [276]. Red wine is a healthier choice than sweet white wine.

The U.K. Chief Medical Officers' Low Risk Drinking Guidelines 2016 (revised from the previous one in 1995) advises that the risks of particular cancers '*starts from any level of regular drinking and then rise with the amounts of alcohol being*

drunk'. It also states that '*there is no level of regular drinking that can be considered as completely safe in relation to some cancers. People can reduce these risks by drinking less than the guidelines or by not drinking at all*' [258].

Many alcoholic and mixer drinks are high in sugar and kilojoules and may contribute to weight gain, so this should be remembered in relation to patients who are already overweight or obese.

Juices

Commercially available fruit juices, where fibre has been removed, are high-sugar foods which cause a sharp increase in sugar in the bloodstream with consequent insulin spike [273]. Juicing of fruits and vegetables is popular and has the advantage of combining a wide range of vegetables including those that may not normally be eaten. If the fibre is filtered out though, the juice should still be a considered high-sugar food. There are machines available which blend the whole fruit including the flesh or pulp, rather than filtering it out, thereby retaining the healthy fibre in the vegetable or fruit. This fibre is useful for healthy bowel function and is essential for the microbiota of the gut.

Eating the whole fruit or vegetable has some distinct advantages. When the whole fruit is eaten, it cannot be consumed so quickly, and it contains fibre, which both delays absorption of sugar and allows a more gradual uptake. In addition, commercially produced fruit juices have lost much of their nutritive value.

There are a few other problems with juicing, including producing doses that are more than are needed, so it is prudent to introduce juicing gradually otherwise it might make the patient feel unwell [273]. Juicing also concentrates the bad parts as well as the good parts, such as the pesticide residues [273]. Thus, it is safer to juice organic vegetables and fruit. It is also better to juice mostly vegetables and add just a small amount of fruit for flavour [273].

Another issue with juicing is the removal of the need for chewing. Chewing is an essential part of the digestive process including the delivery of sufficient quantities of saliva to the food bolus. Also, the pleasure of having the food in the mouth for a longer time and the pleasure of extended periods of taste are reduced with drinking juices.

Soft Drinks

There is not much to be said about soft drinks other than the fact that they provide no nutritional value and are most likely to cause spikes in blood sugar. Consumed on a regular basis, they add to the burden of refined sugars in the body, and a pro-inflammatory condition. They are best avoided. Mineral water and sparkling waters that do not contain added sugars are fine (though excess consumption of

carbonated drinks can lead to abdominal bloating and flatulence). Coating one's red blood cells, protein receptors and cell membrane lipids with sugar is a sure way of wrecking your brain and body.

Principle 9: Avoid Excess Sugar, Artificial Sweeteners and Salt

Excessive sugar in the diet has been linked with many chronic illnesses and contributes to a pro-inflammatory condition within the body, and inflammation is part of the pathogenesis of cancer. High glycidic diets have been found to be associated with increased risk of digestive, endometrial, ovarian and colorectal cancers [11–13, 98]. An increased risk of gastric cancer has been found to be associated with high glycaemic load but not high glycaemic index [14, 157]. Excess refined sugar in diet can lead to weight gain, overweight and obesity, with the attendant increase in risks of diseases such as diabetes and cancer.

High-sugar intake can lead to weight gain and diabetes and these are linked to cancer [273]. When there is insulin resistance, the body compensates by secreting more insulin, and this as well as IGF, can promote tumor growth [285]. Fruit juices contain high amounts of sugar and should be limited. Soft drinks also contain extremely high amounts of sugar and have very little nutritional value, so are best avoided. Excess refined sugar is a feature of a substantial amount of processed foods available in supermarkets and take-away (take-out) foods, as is excessive salt.

Artificial and Natural Sweeteners

Artificial sweeteners can contain dangerous chemical compounds and should also be avoided. Natural sweeteners include Yellowbox honey which has a lower glycaemic index than many other honeys. Manuka honey has been found to have several health benefits.

Salt

The World Cancer Research Fund and American Institute of Cancer Research Second Expert Report states that salt and salt-preserved foods are a probable cause of stomach cancer and recommends avoiding salt-preserved, salted or salty foods, to preserve foods without using salt and limit intake of processed foods that have added salt to ensure that daily intake is less than 6 g (2.4 g sodium) [276]. Excessive salt is also linked to hypertension and increased risk of cardiovascular disease [43].

Principle 10: Avoid Foods Containing Acrylamides

Acrylamide is a chemical used to make polyacrylamide and acrylamide copolymers used as soil conditioners, in wastewater treatment, treatment of drinking water, and in the cosmetic, paper, and textile industries [101, 181]. Acrylamides are also produced by cooking certain foods under conditions of high temperatures (above 120 °C or 248 °F) and low moisture, and can be produced from the amino acid asparagine (found in many vegetables, particularly certain types of potatoes) and reducing sugars such as glucose and fructose, though other pathways may also contribute to their formation [45].

Most acrylamides are formed rapidly during the final phases of baking, frying or grilling of foods rich in carbohydrates such as breakfast cereals, cocoa, coffee, fried potato products (e.g. French fries, potato chips) and bakery products (e.g. biscuits) [45]. Boiling and microwaving are less likely to produce acrylamides than baking, frying or broiling [181]. At high temperatures, longer cooking times can increase acrylamide production [181, 277].

Major contributing foods to acrylamide exposure are:

- fried potato products
- bakery products (biscuits, bread) and
- coffee and solid coffee substitutes [84, 88].

Acrylamides Are Carcinogenic to Humans

Acrylamides have been classified as 'probably carcinogenic to humans' (Group 2A) by the International Agency for Research on Cancer [45] and the European Food Safety Authority 2015 report on acrylamides stated a concern for neoplastic effects based on animal evidence [84], similar to an earlier Joint Food Additive Organisation (FAO) and World Health Organization [277] report on acrylamides [277].

Acrylamides are rapidly absorbed in the body and distributed widely to muscle and all organs. They also make their way into the placenta and breast milk, presenting a significant risk to the unborn child, babies and infants [45]. The concern about the potential for acrylamides to cause cancer is based mainly on the fact that it has been established in animal studies that acrylamides can cause cancer [101, 181]. However, there are several studies in humans that also indicate cause for concern in relation to cancer-causing potential including evidence of an association between acrylamides and significantly higher levels of oestrogen-receptor–positive breast cancer [192], increased risk of postmenopausal endometrial and ovarian cancer,

particularly among never-smokers, but not postmenopausal breast cancer [118] and increased risk (men and women) of renal cancer but not of prostate or bladder cancer [119]. Other potential endpoints for acrylamide toxicity identified from animal studies include neurotoxicity, developmental toxicity and adverse effects on male reproduction [84, 88].

Study of Acrylamide Contamination of Foods:
An Italian study showed that in a sample of 56 breakfast cereals and biscuits, 95.5% of the biscuits and 75% of the breakfast cereals were contaminated, and that 22.7% of biscuits and 33% of breakfast cereals exceeded the values recommended by the European Commission EC 2013/647 (500 μg/kg and 200–400 μg/kg, respectively) [45].

Principle 11: Eat Dark Chocolate (Yes, You Read that Correctly)

For those who love chocolate, research provides a justification on the basis of a range of health benefits to indulge in a couple of pieces of dark chocolate, though of course it is the dark chocolate that is better for you than milk chocolate.

Cocoa, which has a higher content of dark chocolate, contains antioxidant compounds including flavonoids, catechin, epicatechin, proanthocyanidins plus a small amount of fibre. Studies in cells have found that cocoa may have beneficial actions in cancer.

- A study in cells found that high concentrations of cocoa polyphenols extracts have an anti-proliferative effect on prostate cancer cell growth and were able to inhibit growth of metastatic and non-metastatic cell lines [138].
- Another constituent of cocoa, a pentameric procyanidin, has been shown to inhibit the proliferation of human breast cells (this substance has also previously been shown to cause cell cycle arrest in human breast cancer cells) [210].
- When mice were fed for 12 weeks with a high-fat diet supplemented with either a cocoa flavanol extract or a flavanol fraction enriched with monomeric, oligomeric, or polymeric procyanidins, it was found that the oligomer-rich fraction was the most effective in preventing weight gain, impaired glucose tolerance, and insulin resistance [78].

The evidence of health benefits of cocoa and chocolate on the cardiovascular system is growing. Chocolate's benefits include antihypertensive, antioxidant, anti-inflammatory, anti-atherogenic effects, anti-thrombogenic, and an influence on insulin sensitivity [38]. Examples of a diversity of findings about chocolate are set out in Table 3.9.

Table 3.9 Some research findings about chocolate and cocoa

• A systematic review of seven studies (114,009 participants) found that the highest levels of chocolate intake were associated with a 37% reduction in cardiovascular disease and a 29% reduction in stroke compared with the lowest levels [38]
• A small clinical trial has found that mitochondrial structure improved in patients with advanced heart failure and type 2 diabetes after 3 months of treatment with epicatechin-enriched cocoa [248]. This effect on mitochondria might be very relevant if the Metabolic Theory of Cancer is in fact accurate (discussed earlier), and mitochondrial damage is at the root of cancer pathogenesis
• In patients with end-stage renal disease, drinking cocoa flavanols for 30 days was associated partial reversal of endothelial dysfunction, decreased diastolic blood pressure, and acute ingestion of cocoa flavanols mitigated haemodialysis-induced arterial dysfunction (and this effect was sustained throughout the 30 day study) [211]
• An in vitro study that looked at the combination of cocoa extract, fish oil and plant sterols was able to hinder several key steps in the process of atherosclerosis [179]. Lavado cocoa (but not Dutch cocoa) which is high in polyphenols was found to prevent clumping of protein β-amyloid-(Ab) and protect against synaptic defects in mice brains, suggesting that it may be useful in Alzheimer's Disease [271]
• Cacao has been found in animal studies to reduce UV-induced skin wrinkling [144]

Hint: a few squares of dark chocolate half an hour before a meal may help sate the appetite and reduce overeating.

Principle 12: Eat for Your Gut Microbiome

As discussed in Chap. 2, there is increasing evidence of a link between the gut microbiome and cancer. Adequate fibre and resistant starch is important in particular for colon health. Beneficial bacteria within the body assist the digestion of food, produce natural antibiotics, and produce some vitamins. This section will look at fibre, resistant starch, prebiotics and probiotics.

Dietary Fibre

Adequate fibre and resistant starch is needed, in particular for healthy intestinal function. There are both soluble and insoluble forms of fibre.

Dietary fibre is found in vegetables, fruit and pulses (legumes) plus cereals/grains (e.g. wheat, rice, maize (corn), millet, sorghum, barley, oats and rye), roots, tubers and plantains. The protective effect of foods high in dietary fibre may be due to their bulk and relatively low energy density (this may be important in relation to overweight and obesity). The World Cancer Research Fund and American Institute for Cancer Research 2007 Report found convincing evidence that foods such as cereals/grains and peanuts contaminated with aflatoxins are a cause of liver cancer [276]. The Report also concluded that foods containing dietary fibre probably protect against colorectal cancer, and that there is limited evidence to suggest that it may protect against oesophageal cancer.

Dietary Fibre and Colorectal Cancer

The potentially beneficial link between a diet high in fibre and decreased colorectal cancer originated from population-based studies that found differences across countries in colorectal cancer rates [225]. Several case–control studies also found evidence of a lowered risk of colorectal cancer with increased dietary intake of fibre [121, 242, 254], though not all have [249]. However, the evidence in relation to prospective cohort studies and dietary intervention studies of colon adenoma recurrence (which are known precursors to colorectal cancer) has not found as much solid evidence for a protective effect of fibre [3, 148, 225, 249].

Why intervention studies, in general, have not found convincing evidence of a relationship between dietary fibre intake and adenoma or colorectal cancer, particularly when much of the epidemiological evidence and case–control studies have pointed to a protective effect may be due to several factors. These include the multi-stage process of colorectal cancer, plus methodological issues in trials including confounding factors, poor adherence to interventions amongst trial participants and the intention-to-treat analysis design favoured in clinical trials [225]. Poor adherence to clinical trial protocols will dilute results, a fact found when the US Polyp Prevention Trial data was re-analysed. The study originally found no difference between recurrence of colon adenomas at the end of a 4-year study (testing the efficacy of a low-fat, high-fibre and high fruit and vegetable diet), but on re-analysis of the data they found a 35% reduction in the odds of adenoma recurrence in those who were the most adherent participants. Thus, high compliance with a low-fat, high-fibre diet was found to be associated with decreased risk of recurrence of adenoma [225]. This re-analysis highlighted an important point in interpretation of study results—reporting compliance with the study intervention is vital, as is interpretation of the results in relation to compliance.

Rates of colon cancer are known to be much higher in African Americans than in rural South Africans (65 per 100,000 compared to <5 per 100,000), and these higher rates are associated with a diet higher in animal protein and fat and lower in fibre, as well as higher colonic secondary bile acids, lower colonic short-chain fatty acids and higher mucosal proliferative biomarkers of cancer risk. A study was conducted where, for 2 weeks, a cohort from each of these populations swapped diets, under close supervision. The study found reciprocal changes in mucosal biomarkers for cancer risk in each group, as well as in aspects of the microbiota and metabolome that are known to affect cancer risk. In the African American group, secondary bile acid synthesis was suppressed [190].

Certainly, there is some indication from animal experiments of mechanisms by which fibre might prevent tumors. For example, rat experiments have demonstrated that high levels of butyrate obtained following fermentation of soluble dietary fibre was found to inhibit early and late events in colon tumorigenesis by controlling key pathways in cell apoptosis [18].

Fibre and Other Cancers

There is some evidence that fibre may protect against breast cancer [90, 92, 198] and it may be protective against mouth, throat and oesophageal cancers [238]. A recent study found that early adulthood total dietary fibre intake was associated with a significantly lower risk of breast cancer, and that both higher intakes of soluble and insoluble fibre were both associated with lower risk. Higher intake of dietary fibre in adolescence was significantly associated with lower breast cancer risk also [90], underscoring the importance of diet in childhood as well as adulthood. A meta-analysis of 10 prospective studies found a significant inverse relationship between breast cancer risk and dietary fibre intake [77].

How fibre exerts its beneficial effects in breast cancer may be partially due to the fact that high-fibre diets are typically lower in fat, and dietary fat is believed to increase risk of breast cancer [260]. In addition, fibre binding to oestrogen in the digestive tract helps expedite the removal of excess oestrogens [204].

Other Benefits of Fibre

Fibre creates a sense of fullness and thereby helps satiate our appetites [42]. It thus may have some advantages in terms of reducing amount of food consumed and therefore weight control. Contrary to past fears, fibre doesn't appear to interfere with iron absorption. The China Study, mentioned earlier in this chapter, found no evidence of this, despite the average fibre intake being about three times higher in rural China compared to the US. In fact, they found the opposite. Average iron intake in rural Chinese was 34 g/day compared with average American intake of 18 mg/day and it was much more associated with plant-based foods than

animal-based foods. Thus, consuming more plant-based foods and therefore more fibre was associated with greater iron consumption, not less [42].

Resistant Starch

Resistant starch is distinct from dietary fibre, and is the total amount of starch and the products of its degradation that resist digestion in the small intestine. Resistant starch is fermented by the bacteria in the large intestine, producing several benefits:

- Increasing stool bulk
- Promoting a mild laxative effect
- Encouraging growth of healthy bowel bacteria (acts as a prebiotic)
- Producing short-chain fatty acids including butyrate which promote a healthy bowel
- Preventing degradation of the mucous layer of the large intestine, which protects colon cells
- Reducing intestinal pH and the production of harmful secondary bile acids, ammonia and phenols
- Reducing the glycemic response [156]

Resistant starch and colorectal cancer

Resistant starch produces butyrate which has been shown to reverse neoplastic changes in colon cells [93]. Consumption of resistant starch decreases ammonia and other nitrogen-containing compounds [29] which are related to increased colon cancer risk [30].

Animal studies indicate that high-resistant starch diets may prevent colon cancer [215]. An early observational study found a linear correlation between starch intake and reduced risk of colorectal cancer (but not between dietary fibre intake and colorectal cancer) [48]. A study in South Africa found that those consuming high levels of maize porridge containing high levels of retrograded resistant starch and low levels of dietary fibre had significantly lower levels of colorectal cancer in comparison to another population who consumed higher levels of dietary fibre, but lower levels of resistant starch, which may suggest that the fermentation of resistant starch was able to confer protection [2].

Sources of resistant starch

Some sources of resistant starch that contain at least 1 g resistant starch per 100 g as eaten include: grains (e.g. millet, barley, oats), breads (pumpernickel, rye, black, white fibre increased), English-style muffins, some breakfast cereals (e.g. processed bran, low-sugar puffed flakes), bananas (green bananas have a much higher content than ripe), mature legumes and pulses (e.g. soy, lentils, split peas), baked beans and corn bread [156].

Table 3.10 Some sources of prebiotics and probiotics

Sources of prebiotics	Sources of probiotics
Onion, garlic, leek, honey, artichokes, soy, wheat, barley, oats, almonds, pistachios, bananas, skin of apples, beans, seaweed and marine microalgae, asparagus, chicory root, acacia gum, raw chicory root, raw honey, whole grain corn, psyllium husk	Fermented foods such as yoghurt, soured milk products, kefir, fermented vegetables such as sauerkraut and kimchi

Based on data from Landon et al. [156], de Jesus Raposo et al. [66], Dr. Axe [80], International Food Information Foundation Council [128]

Prebiotics and Probiotics: What Are They?

A **prebiotic** is defined as 'a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health' [106]. A prebiotic food is one that escapes digestion and absorption in the small intestine and upon reaching the large intestine, changes the composition or activity of the microbiota selectively, conferring a health benefit [106]. Prebiotics are specialised plant fibres including skin of apples, bananas, onions, garlic, and beans that feed that good bacteria in the large intestine. Many resistant starches act as prebiotics, though not all resistant starches qualify as prebiotics [156]. Prebiotics are needed to feed the good bacteria that make up the gut microbiome.

Probiotics are live bacteria in yoghurt, other fermented dairy products (e.g. kefir) and commercially produced supplements.

See Table 3.10 for some sources of prebiotics and probiotics.

How Do Probiotics Work?

Probiotics are able to boost immunity, eliminate pathogens, moderate effects of antibiotics, aid in digestion and inflammatory bowel disease and can play a role in prevention and treatment of cancer.

Impact on cancer pathogenesis

Lactic acid bacteria are a heterogenous group of microorganisms present in many foods like yoghurt and are often used as probiotics [8, 69]. Some of the actions by which probiotics and the lactic acid bacteria may impact in cancer include prevention of mutations, inhibition of mutagenic activity, decreasing enzymes implicated in the generation of carcinogens, mutagens or tumor-promoting agents, anti-genotoxicity, anti-inflammatory, ridding the body of mutagens, delaying the onset of tumors, suppressing tumors and modulating the immune response including immune cell surveillance [69, 151, 200, 275].

Probiotics and modulation of immune response

Lactic acid bacteria are able to induce modulation of cell-mediated immune responses, activate the reticulo-endothelial system, augment cytokine pathways and regulate interleukins and tumor necrosis factors [151].

Experiments in mice suggest that probiotics such as Bifidobacterium may be able to modulate cancer immunotherapy via facilitation of infiltration of T Cells into tumors, and are able to almost completely halt melanoma growth when combined with a specific antibody therapy [237]. Another study in mice with chemically induced colon tumors found that feeding the mice yoghurt for 6 months resulted in inhibition of tumor growth, and an increased number of IgA-secreting cells and CD4 + T lymphocytes and a decrease in IgG+ and CD8+ cells in the large intestine walls. The researchers concluded that yoghurt may be modulating the immune response by either stimulating the production of cytokines when required or inducing down-regulation of immune cells to avoid an exaggerated immune response [69].

Oral administration of probiotic microorganisms is able to affect mucosal sites outside the colon, as B and T cells can migrate from Peyer's patches to other mucosal membranes around the body (e.g. respiratory, gastrointestinal, genito-urinary tract) as well as to exocrine glands (mammary, prostatic, salivary, lacrimal) [35].

Probiotics and Infection Prevention

Since infections in those who are immunocompromised can add to the burden of cancer patients, and the gut microbiome plays a role in immunity, probiotics may have a role to play in helping prevent infection [213]. It is important that studies of safety and efficacy are conducted [213]. Current advice is for neutropenic cancer patients to avoid probiotic products; however, this advice is based on case reports of bacteraemia and manufacturer's advice and not on solid scientific evidence [213]. It may be found by future research that probiotic supplementation is essential in this cohort of patients.

A systematic review of 17 studies of probiotic use in 1530 cancer patients (756 consuming probiotics, 774 not consuming them) found 105 adverse events in those consuming probiotics and 145 adverse events in those not consuming them. They were unable to establish whether the reported adverse events were associated with probiotic consumption or other causes, and did note that there were five cases of probiotic-related bacteraemia/fungaemia/positive blood cultures [213].

Probiotics and Breast Cancer

In a meta-analysis of 22 prospective cohort studies (1,566,940 participants) and five case–control studies (33,372 participants), intake of yoghurt (and low-fat dairy, but

not other types of dairy) was found to be significantly associated with lower risk breast cancer [287]. A case–control study found that consumption of drinks containing *Lactobacillus casei* Shirota and soy isoflavone was found to be inversely associated with breast cancer in Japanese women who had consumed this regularly since adolescence [250]. The combination of the two seems to be beneficial—rat experiments have shown that soy milk can prevent development of mammary tumors whilst *L. casei* Shirota is able to suppress tumor growth [140].

Studies in breast cancer mice models found that kefir contains several substances that have an immunomodulatory capacity and prevent particular types of cancer [267], as well as retard tumor growth (the mechanisms involved included decreased cytokine IL6 and increased IL10 [68] and increase apoptosis [70]). What was interesting was that the tumor-preventing activity was due to substances released during the fermentation process and not the microorganisms themselves [68]. Other research has shown that lactic acid bacteria supplementation inhibited tumor development in mice through stimulation of the host immune cells, by triggering of CD4+ CD25+ lymphocytes. When these cells were transplanted into other mice, they conferred anti-neoplastic protection in the recipients [154].

Probiotics and Colon Cancer

There is growing evidence of the role of lactic acid bacteria in prevention of colorectal cancer, with a wide range of studies indicating that lactic acid bacteria can interfere with cancer pathogenesis pathways [292]. Lactic acid bacteria have been found to inhibit colorectal cancer initiation or progression through multiple pathways [292]. There are several potential mechanisms by which lactic acid bacteria may play a role in preventing or retarding colon cancer including influencing the metabolic, immunologic and protective functions of the large intestine [275], for example, modulating the intestinal microbiota, inactivating carcinogenic compounds, inducing apoptosis, antioxidant effects and via epigenetic mechanisms [8, 292]. Ingestion of prebiotics also increases the number and activity of lactic acid bacteria in the human colon [275]. Lactic acid bacteria and prebiotics that enhance them are able to deactivate genotoxic carcinogens [275]. In addition, probiotics may be able to provide protection against colon cancer by suppressing the expression of COX-2 [269].

Other Cancers

Lactobacillus species have been found to be associated with promotion of clearance of Human Papilloma Virus-related abnormalities in cervix cells [264] and in animal studies, lactobacillus has been found to inhibit fibrosarcoma tumor growth, activating macrophages and high levels of TNF-α [202], and protect against liver cancer [150], detailed elsewhere [8].

Concomitant Use in Chemotherapy

Probiotics may help alleviate some of the side effects of chemotherapy. Patients undergoing chemotherapy who were administered Bifidobacterium breve strain Yakult had reduced frequency of fever and a lower use of antibiotics than a comparison placebo group. Those in the placebo group also had greater disruption of their intestinal microbiota after chemotherapy including an increase in levels of Enterobacteriaceae compared with the probiotic group [268].

Diarrhoea can also be a side effect of chemotherapy as well as antibiotic therapy, and can contribute to increased hospital admissions in cancer patients [213]. A systematic review found that probiotics may decrease the frequency and severity of diarrhoea in cancer patients, as well as need for anti-diarrhoeal medication, though more studies are needed [213].

Principle 13: Avoid Foods that Interfere with Sleep

Certain foods can interfere with sleep and are best either avoided, or eaten earlier in the day. Many people with cancer have problems with sleep. Sleep is vital for the body and mind's regeneration (see Chap. 4 for more details).

Examples of foods and beverages to avoid if a patient does have problems sleeping include very spicy foods, energy drinks, teas and coffee, alcohol, soft drinks and cheeseburgers. See Chap. 4 (Table 4.3) for more details.

Principle 14: Pay Attention To Food Cooking and Storage Methods

Some food preparation processes such as salting, smoking, charcoal-cooking and broiling are carcinogenic [75]. The World Cancer Research Fund and American Institute of Cancer Research Second Expert Report found that processed meat is a cause of cancers of the oesophagus, lung, stomach and prostate [276].

The report also stated that Cantonese-style salted fish is a probable cause of nasopharyngeal cancer [276].

Cooking Meat

The World Cancer Research Fund and American Institute of Cancer Research Second Expert Report found that there is 'limited evidence' that animal foods that are grilled/broiled, barbecued/charbroiled) or smoked are a cause of stomach cancer [276].

When muscle meat (beef, pork, poultry, fish) are cooked at high temperatures, heterocyclic amines are formed (from amino acids and creatine) and these can pose a cancer risk. The cooking methods that produce the largest amounts are frying, grilling (broiling), and barbecuing (charbroiling) as these use very high temperatures. Meats cooked via oven roasting and baking involve lower temperatures, and therefore produce less heterocyclic amines (though be warned, the gravy from meat drippings contains substantial amounts). Meats that are partially cooked in a microwave oven before being cooked by other higher temperature methods also have lower levels of these chemicals [276].

Polycyclic aromatic hydrocarbons (PAHs) are formed when meat is burnt incompletely. When meat or fish is cooked with intense heat over a direct flame e.g., grilling (broiling) or barbecuing (charbroiling), fat dripping onto the hot fire produces PAHs that can stick to the surface of the food, and the higher the heat, the higher the level of contamination. Using wood creates more PAHs than charcoal [276].

Hint for Cooking Meat
Cooking at lower temperatures is generally a healthier method of cooking meat than cooking at higher temperatures.

Cooking and Acrylamides

As discussed previously under **Principle 10** Avoid Foods Containing Acrylamides, cooking particular foods at high temperatures (>120 °C) can create dangerous acrylamides.

Microwaving

Care should be taken with microwaving food—plastic containers that are not microwave safe and plastic wrap covering foods should be avoided as they can produce toxins. If food is microwaved at higher or prolonged temperatures, or if water is added, this can destroy nutrients. Non-stick pans can also release toxins if the surface is damaged or temperature too high [273].

Cooking and Nutritional Value

In general, the less processed the food is, the more nutrients it retains and the better it is for you. Most forms of cooking reduce the overall nutrient content of

vegetables. Raw foods retain the most nutrients, then in order: steamed, baked, boiled and fried (least retention). Boiling liberates 50% of important nutrients into the water. However, cooking also increases the bioavailability of some nutrients and therefore some foods should be cooked (see next section).

Vegetables should be lightly cooked, for example steaming for 5 min to soften them whilst still retaining the nutrients. Brief scalding in hot water is fine, but prolonged boiling should be avoided. Roasting or grilling or briefly stir frying are also acceptable methods of cooking to retain flavour and nutrients. Stir frying at high temperatures for lengthy periods should be avoided as it destroys many of the nutrients. If frying, it should be done quickly with either water, or with oils with a high smoke point (high heat tolerance) such as sesame oil, rice bran oil or macadamia nut oil.

Some Foods Should Be Cooked

Some foods are better cooked as it increases the bioavailability of key constituents. The bioavailability of carotenes, for example, is increased by cooking and pureeing vegetables, in particular by adding oil since carotenes are fat soluble [276].

Cooking and processing tomatoes increases the concentration and bioavailability of one its key active constituents, lycopene, and when cooked and eaten with oil-rich foods, this greatly increases its absorption from the digestive tract [273, 276]. Lycopene is four times more bioavailable when derived from tomato paste than from fresh tomatoes [276].

Cooking with Oils

The smoke point of oils is the temperature beyond which it begins to smoke and gives off toxic smoke. A high smoke point is desirable if you are going to cook (fry) with oils. The smoke points if several oils are set out in Table 3.11.

Table 3.11 Smoke points of common oils

Oil	Smoke point
Olive oil	210 °C [193]
Sesame oil	210 °C [193]
Grape seed oil	252 °C [193]
Avocado	249 °C [193]
Macadamia nut oil	196 °C [193]
Coconut oil	177 °C [24]
Rice bran oil	254 °C [24]

Some Wisdom from the Orient: Eating from the Chinese Medicine Perspective

Many in the west advocate eating raw vegetables in preference to overcooked vegetables. From a Chinese medicine perspective, however, raw and cold foods can be damaging to the digestive system (termed the Pi and Wei in Chinese, which translates to 'Spleen' and 'Stomach' respectively, the Spleen being an entirely different concept in Chinese medicine than what it is in biomedicine). When a person has cancer, particularly if they have undergone treatment such as chemotherapy, it is likely that their 'Spleen/Stomach' has become weakened. If this was the case (and this would need to be diagnosed by a Chinese medicine practitioner), then raw foods and cold foods (e.g. ice cream, salads, raw juices) should be minimised or avoided and instead warm, cooked foods eaten. Raw juicing would be considered potentially damaging to the 'Spleen/Stomach' if consumed excessively.

The Bigger Picture: Health Information and the Forces at Play

At the systemic level, there are some strong forces at play in the world of food, as there are in medicine—these are the companies that make billions of dollars from people consuming their products and it's not just the obvious fast-food chains. These companies and people who control them have a vested interest in the kinds of information that reach the public, and their marketing is fierce and convincing. As clinicians, we need to be aware that big food organisations play a big part in determining national dietary guidelines and ensuring that these don't damage their business. For many years, the Australian and other national heart foundations in other countries were warning us that butter, cheese and eggs were no good for cardiovascular health. Now, the Australian and other international guidelines deem these not so detrimental to our health. We only have to remember the influence that the cigarette industry had, with medical doctors advertising cigarettes as being soothing for the throat in the middle of last century, despite the fact that German scientists had already identified that smoking was a cause of lung cancer decades previously.

Additionally, in the world of medicine, there is big money in cancer, as there is in other chronic illness. The Pharmaceutical Industry may not be so welcoming to programs and incentives promoting nutrition as a preventative and/or adjunct treatment to cancer. This is substantiated by the very minor role that diet plays in medical degrees, medical journals and, in particular, in medical research. This is a strong indication of the value status given to nutrition and its role in prevention and treatment of disease.

Voicing Concerns About Contamination of Our Food Supply

Unfortunately, what types of foods we are able to procure on a daily basis is not always within our control and the information about it can be confusing and contradictory. We are, for the most part, dependent on others for our food, and more and more, that food supply chain is becoming adulterated or it is nutritionally lacking. Where we live and our socioeconomic situation also impact on what kinds of foods we can buy for ourselves. Organic foods, for example, are more expensive and hard to find in some places. As healthcare practitioners, we have a role to play in voicing our concerns about the impact of environmental toxins on our food supply, as do our patients. Who else will stand up if we don't?

Reductionism in Research

As clinicians, we need to understand how research is conducted and how to interpret it. Our scientific research methods are inherently reductionist in nature. If we apply this reductionism to the study of nutrition, when we try to isolate active constituents in foods instead of looking at whole foods and combinations of foods as diets, we are likely to miss some very important information. Single nutrient studies, though essential for understanding their function, are often not very useful for the clinician with a patient who has nutrient-related problems. Importantly, the importance of the social benefits of eating with others, such as the opportunity to unload stresses, should not be underestimated, though this is rarely considered in dietary studies.

Conclusion

At the end of it all, a healthy patient will do better than an unhealthy one, no matter what the health disorder. Research supports the notion that if you improve your diet, you will live longer. Nutrition is one of the essential pillars of health, along with stress reduction, sunshine (vitamin D), physical activity and sleep. Diet is one modifiable factor in people's lifestyles that can contribute to prevention of cancer, and in a person with cancer, their road to recovery. However, it is difficult for people to change their diets as diets are habits, typically lifetime habits. Thus, changing diet is about practice—practising new habits. Practice makes perfect and it takes discipline, not unlike the discipline of sportswomen and sportsmen who train day in and day out. One trick is for the patient to make one small change every day and reward herself/himself for making that change. The size of the reward

should be greater than the degree of change. A simple, individualised strategy on paper, for example incorporated into a Wellness Plan, works well.

We, as clinicians, are there to give guidance, using the best evidence we have, and to play the role of the coach also, encouraging our patients to make steps, however incremental, toward a better lifestyle that includes a healthy diet. Eating should be pleasurable. There is no point in imposing strict dietary measures on a patient if, in the end, it will just make them miserable. Some common sense needs to prevail. The social context of eating, with friends and family, where stresses can be unloaded, is likely to be almost as important as what one eats, yet it is rarely thought of when diet is considered. Please consider.

Additional Reading Section

- **Omega 3 and Omega 6 (Section: Principle 7 Include Good Sources of Dietary Fats and Oils and Avoid Unhealthy Ones)**
- **Green Tea (Section: Principle 8 Keep Hydrated But Choose Your Drinks Wisely, Sect. 8.3)**.

Section Principle 7: Include Good Sources of Dietary Fats and Oils and Avoid Unhealthy Ones

Omega 3 and Omega 6

More On the Evidence that $n-3$ PUFAs Decrease Risk of Cancer

Population studies indicate that the incidence of prostate cancer is high in North America and northern Europe but low in Asia. In Japan, intake of $n-3$ PUFAs is around eight times that of Americans (and blood levels are twice that of Americans); however, prostate cancer rate was 22.7 per 100,000 in 2008 compared to 83.8 per 100,000 in the US [278]; in 2012, the prostate cancer incidence was 13.6% in Japan compared to 28.3% in the US [279]. Conversely, a 2013 study found that higher blood levels of Omega 3 were associated with increased risk of prostate cancer [36], however, the study has been widely criticised on a number of levels and was methodologically flawed [1]. A more recent review found that cohort studies suggested an association between higher intake of fish and decreased risk of prostate cancer-related death. It concluded that overall, there was insufficient evidence to suggest a relationship between fish-derived $n-3$ PUFAs and prostate cancer risk; however, an association between higher $n-3$ PUFA intake and decreased prostate cancer mortality may be present, and more studies were needed [10].

Not all the evidence is positive, and an earlier systematic review found that Omega-3 intake was not associated with incidence of various cancers with the reviewers concluding that dietary supplementation with $n-3$ PUFAs was unlikely to prevent cancer [169]. A likely reason for this is that simply not enough $n-3$ PUFA's were consumed. Where supplements are involved, the quality of the supplements is very important and may impact results substantially.

Anti-cancer Mechanisms of $n-3$ PUFAs

Omega-3 fatty acids are likely to exert anti-cancer effects by impacting several different pathways associated with cancer pathogenesis including cell proliferation, cell survival (including promoting apoptosis), angiogenesis, inflammation, metastasis and epigenetic abnormalities [136].

Several studies have demonstrated that $n-3$ PUFAs, EPA and DHA, can inhibit tumor growth by inducing cancer cell apoptosis, alone or synergistically when combined with conventional chemotherapy (where they may improve efficacy and/or tolerability) [56, 64]. The cytotoxicity of $n-3$ PUFAs is confined to cancer cells—research indicates little or no toxicity to normal cells—and it has the potential to sensitise tumor cells, potentially improving their efficacy [64]. Both EPA and DHA have anti-inflammatory properties and are able to decrease arachidonic acid-derived eiconsanoids and decrease production of pro-inflammatory cytokines as well as decreasing reactive oxygen species and lymphocyte proliferation [214].

PUFAs have a regulatory ability and can both inhibit or facilitate apoptosis depending on the circumstances. They selectively affect the Toll-Like Receptor family and influence the activity of NFκB downstream. NFκB is a transcription factor that is active in most tumor cells (hematopoietic, prostate, breast cancers), and controls genes involved in apoptosis, inflammation, cell adhesion, proliferation, the adaptive immune response, the stress response, and tissue remodelling. Disruption of NFκB signalling leads to inflammatory diseases and cancer. In tumors, suppression of NF-kB activity inhibits proliferation, causes cell cycle arrest, and leads to apoptosis [60].

Omega-3 oils are also beneficial for brain function and mental health, cardiovascular function, and protection against inflammatory disorders.

Benefits of $n-6$ PUFAs

$n-6$ linoleic acid, found in many plant oils, is metabolised to γ-linolenic acid (GLA) which is converted to dihomo-γ-linolenic acid (DGLA). DGLA is a precursor to prostaglandin PGE1 (involved in inhibition of platelet aggregation and inflammation, produces vasodilation, regulates immune responses and reduces blood pressure and inhibits cholesterol biosynthesis) and 15-OHDGLA which inhibits formation of pro-inflammatory compounds from arachidonic acid (e.g.

PGE2 and 4-series leukotrienes) [96]. DGLA is also converted to arachidonic acid through the action of D-5 desaturase; however, because human D-5 desaturase has limited activity, production of PGE1 and 15-OHDGLA from DGLA is preferred over production of arachidonic acid. Arachidonic acid is then converted to EPA, and EPA is then converted to DHA [96]; however, arachidonic acid can also produce a range of pro-inflammatory compounds [96].

Dietary forms of GLA include evening primrose oil, borage oil and blackcurrant seed oil as well as other foods [96]. Dietary GLA reduces the synthesis of potent inflammatory mediators from arachidonic acid [214] and has been found to be beneficial in a range of health conditions including general inflammation, hypertension, diabetic neuropathy, rheumatoid arthritis and skin conditions [96]. Arachidonic acid does play useful roles, however, including helping make up cell membranes and is used within the body to make substances involved in regulating inflammation, blood clotting and cell communication.

Critical Ratio of *n* − 3: *n* − 6 PUFAs

Despite *n* − 3 and *n* − 6 PUFAs both having a range of beneficial actions in the body, the ratio of *n* − 6: *n* − 3 is important. The major sources of *n* − 6 and *n* − 3 PUFAs, linoleic acid and α-linolenic acid respectively, are desaturated by the same enzyme human D-6 desaturase, leading to competition between the two fatty acid groups [214]; this enzyme is often impaired in the western diet and generally favours the *n* − 3 pathway [96].

High levels of *n* − 6 PUFAs or a high *n* − 6: *n* − 3 PUFA ratio promotes inflammatory conditions and diseases such as cancer and cardiovascular disease, whereas increased levels of *n* − 3 PUFAs or a low *n* − 6: *n* − 3 PUFA ratio is suppressive for such conditions [235].

Western diets are excessive in the amount of *n* − 6 and deficient in *n* − 3 PUFAs with the ratio of *n* − 6 to *n* − 3 PUFAs 3 in western diets somewhere between 10:1 or 25:1 [235, 236, 273]. In contrast, it is likely that humans evolved on a diet where this ratio was 1:1 [235]. In patients with colorectal cancer, a diet characterised by a ratio of 2.5:1 (*n* − 6: *n* − 3 PUFAs) reduced rectal cell proliferation; however, a ratio of 4:1 had no effect in reducing rectal cell proliferation. The optimal ratio is likely to differ from disease to disease [235].

Section Principle 8 Keep Hydrated But Choose Your Drinks Wisely Section "Tea"

Tea and Cancer

There have been only a few randomised controlled trials, two of which examined the effects of tea on urine levels of 8-hydroxydeoxyguanosine (8-OHdG), a

biomarker of oxidative DNA damage that may be a predictor of increased cancer risk. In one, 133 adult heavy smokers were randomly assigned to drink four cups of either decaffeinated green tea, decaffeinated black tea, or water daily for 4 months. Green tea drinkers had a significant (31%) decrease in urinary levels of 8-OHdG whilst there was no change in black tea drinkers, indicating that green tea may protect smokers from oxidative damage and reduce cancer risk caused by smoking-associated free radicals [111].

In another study, 124 individuals at increased risk of liver cancer due to hepatitis B virus infection and aflatoxin exposure were randomised to receive either 500 mg (equivalent to two cups of tea) or 1000 mg of a green tea polyphenol supplement or a placebo daily, for 3 months. Both green tea supplement groups had substantially lower urinary 8-OHdG levels at the study, suggesting that green tea polyphenols are effective in reducing oxidative DNA damage [168].

Cell culture research demonstrated that black and green tea extracts have anti-mutagenic, anti-proliferative and anti-neoplastic activity. Both black and green tea extracts were able to inhibit neoplastic transformation in mouse mammary organ cultures, rat tracheal epithelial cells and human lung tumor epithelial cells, and were able to strongly inhibit benzo[a]pyrene adduct formation with human DNA, as well as enhance induction of phase II enzymes, glutathione-S-transferase and quinone reductase and inhibit free radicals [240]. Studies in humans have found external application of green tea extract protects against UV(B) damage [83].

Green tea may be beneficial in other conditions including hypercholesterolemia, artherosclerosis, Parkinson's disease, Alzheimer's disease, and other ageing-related disorders [288].

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Chapter 4
Sleep

In this chapter we explore:

- Why we need sleep
- Common sleep disorders such as insomnia and chronic sleep restriction
- Health risks of poor sleep
- How poor sleep can contribute to cancer
- Potential mechanisms by which poor sleep may contribute to cancer pathogenesis
- The potential role of electric light, electromagnetic waves and shift work on sleep, circadian rhythms and cancer pathogenesis
- Strategies to improve sleep

Introduction

Sleep disorders can be prevalent in any socioeconomic group or occupation. Sleep problems are linked with the introduction of the light bulb and artificial light, which has dramatically shifted our typical sleep-awake patterns so that we no longer 'rise and retire with the sun'. Add to that shift work, international business with its mismatched time zones, and a pervasive cultural shift to overwork and being available 24/7 and you have a recipe for high stress and poor sleep in the industrialised countries. Our present culture of sleep deprivation can push us past our biological capacity.

Good sleep is vital for our health and well-being. Poor sleep is associated with a myriad of ill health conditions, including cancer and several of its risk factors. There is evidence that it may contribute to the development of cancer and much research has been conducted to investigate the mechanisms by which this may occur. Some of this will be discussed briefly later in this chapter.

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After a patient is diagnosed with cancer, what then? Whilst sleep is only one factor of many that may have led the patient to a state of imbalance whereby cancer has manifested, it is nonetheless an important one and needs to be discussed with the patient, and on more than one occasion. As a person mentally processes a diagnosis of cancer, this can lead to considerable anxiety and disrupt sleep. Cancer treatments themselves can interfere with sleep. If a patient with cancer is sleeping poorly, this can continue to contribute to poor health. So, it is important to continue to check in with the patient on their sleep.

In This Chapter

In this chapter, we will explore what normal sleep is, why we need sleep, the common sleep problems of insomnia and chronic sleep restriction, the health risks of poor sleep, and the relationship between sleep and cancer, including some of the underpinning pathological mechanisms. Finally, since there are many strategies available that may assist with sleep, we will explore some strategies that might be discussed with the patient as part of an integrative consultation.

What Is Normal Sleep?

Healthy sleep consists of two types of sleep that alternate through the night: non-rapid eye movement (non-REM) sleep which comprises about 75–80% of sleep time, and REM sleep, which accounts for the remaining 20–25% [20].

Non-REM sleep was classically subcategorised into four stages (1–4), though this has been revised to Stages N1, N2 and N3 (combines stages 3 and 4), which parallel depth of sleep (arousal thresholds are lowest in stage N1, with N3 being the deepest level). The N3 stage is known as 'slow wave sleep'. There is usually minimal or only fragmentary mental activity, low muscle activity and minimal physiological activity during non-REM sleep [20]. In addition, body temperature drops, and heart rate and breathing slow during non-REM sleep. The deepest stage of non-REM sleep produces physiological changes that increase immune system functioning [57].

REM sleep, in contrast, is characterised by an increase in brain activity with active dreaming, decreased muscle tone (spinal neurons are inhibited by the brainstem, suppressing muscle tonus), variable heart and respiratory rates and rapid eye movements [20]. REM sleep is considered vital to health and many sleep disorders, including a lack of sleep, are problematic because of their impact on the REM cycle sleep.

Sleep normally begins in non-REM and progresses through stages N1, N2 and N3 (deepest) then 80–100 min later, the first REM sleep occurs. Non-REM and

REM then cycle every 90 min, with the deeper stage N3 of non-REM (also called slow wave sleep) concentrating in the early non-REM cycles, and the length of the REM sleep episodes lengthening as the night progresses [20].

Sleep needs change over our lifetime

Our needs for sleep change over our lifetime. Newborns enter active sleep (REM sleep) before quiet sleep (non-REM) and have a shorter sleep cycle of around 50 min. At birth, REM sleep constitutes about half of total sleep but by age 2, REM only constitutes 20–25% of total sleep. Also, newborns do not have non-REM slow waves—these develop in the first 2 years of life. Slow wave sleep (Stage N3 of non-REM sleep) decreases across adolescence by 40% from preteen years and continues to decrease thereafter, albeit at a slower rate, through to old age [20].

Other factors affecting sleep

Several other factors can also affect sleep and these include previous sleep-wake history, dementia, phase of the circadian timing system, ambient room temperature, drugs, and sleep disorders [20]. About 13–33% of the Australian adult population have regular difficulty either getting to sleep or staying asleep [29].

Why Do We Need Sleep?

Sleep is an integral part of our biological rhythm. These rhythms are essential for health and wellbeing and provide cyclical times in which the body can perform a whole range of complex hormonal and neurochemical processes that help keep us healthy. While we are asleep our bodies repair DNA, build and repair muscles and tissues, and regulate weight and mood chemicals. Bodily functions that are impacted by sleep include:

- Hunger and appetite (via hormones leptin and ghrelin)
- Processing of memories and newly learned tasks
- Ability to perform complex and abstract tasks using higher cortical functions
- Regulation of hormone levels (e.g. Growth hormone, which is critical in fat breakdown, liver regeneration and normalisation of blood sugar)
- Regeneration of cells including muscles and tissues, liver regeneration
- DNA repair
- Weight regulation
- Regulation of mood chemicals and behaviour

Sleep is restorative and is vital for recovery from daily stresses and strains [170] as well as regulation of emotions [131]. Any changes in sleep are likely to affect physical and mental health, in particular when disease is present [2]. A good night's sleep is essential to the emotional brain; sleep deprivation makes people more sensitive to emotional and stressful situations and stimuli [170]. REM sleep, in particular, affects next day moods and emotions [170].

Sleep is believed to play an important role in memory, learning and neural plasticity, and there are several theories of how sleep-dependent plasticity might be involved in functional recovery from various neuropsychological conditions including obstructive sleep apnoea, amongst others [51].

How Much Sleep Do We Need?

Australian sleep experts have adopted new guidelines from the United States on how much sleep people need at various life stages. The evidence-based guidelines from the US National Sleep Foundation (https://sleepfoundation.org/how-sleep-works/how-much-sleep-do-we-really-need) recommend young and middle-aged adults get 7–9 h sleep a night, but this does not have to be unbroken. The breakdown of hours per day for each age group is:

- Newborns (0–3 months): 14–17 h
- Infants (4–11 months): 12–15 h
- Toddlers (1–2 years): 11–14 h
- Preschoolers (3–5 years): 10–13 h
- School children (6–13 years): 9–11 h
- Teenagers (14–17 years): 8–10 h
- Younger adults (18–25 years): 7–9 h
- Adults (26–64 years): 7–9 h
- Older adults (65+ years): 7–8 h

Both too little and too much sleep can negatively affect health, discussed shortly. Contrary to popular belief, we cannot 'catch up on lost sleep' on the weekend, and we are often unable to realise just how mentally impaired we are by our sleep deficit. We need to learn to sleep naturally again, and make it our health goal to awaken refreshed each morning, without the invasion of stress-inducing alarm clocks.

Ralph Waldo Emerson said, '***Finish each day before you begin the next, and interpose a solid wall of sleep between the two***'.

His advice not only underlines the importance of good sleep, but also provides us with a terrific mantra for optimal health.

Common Sleep Problems: Insomnia and Chronic Sleep Restriction

The most common sleep disorder is insomnia which affects a significant proportion of the general population. Other types of sleep-wake disorders include hypersomnolence disorder, narcolepsy, breathing-related sleep disorders (e.g. sleep apnoea),

circadian rhythm sleep-wake disorders, restless legs syndrome, nightmare disorder, non-rapid eye movement sleep arousal disorders, rapid eye movement sleep behaviour disorder and substance/medication induced sleep disorder [3].

Definition of Insomnia

The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) defines insomnia as difficulty getting to sleep, staying asleep or having non-restorative sleep despite having adequate opportunity to sleep, together with associated impairment of daytime functioning, with symptoms being present for at least 4 weeks [3].

Categorisation of Insomnia

Insomnia is sub-categorised as acute or chronic. Acute insomnia occurs over a duration of less than 4 weeks, generally triggered by a precipitating event, and once the event passes, normal sleep returns [3, 29]. Chronic insomnia is insomnia that continues for more than 4 weeks [3], and it tends to form a pattern of relapse and remission rather than resolving [106].

Chronic Insomnia

Chronic insomnia affects 9–15% of the general population worldwide, with a prevalence of approximately 6% in countries of high income [119]. Chronic insomnia has a genetic component, with hereditary coefficients of 42–57%, and women suffer more from insomnia than men at a ratio of 1.4:1 which increases to 1.7:1 over the age of 45 years [134]. More than 50% of insomnia cases are due to psychological factors including stress and anxiety.

Other Terms for Causes of Sleep Loss: Chronic Sleep Restriction, Total Sleep Deprivation and Sleep Disruption

There is another term in the scientific or research literature, ‘chronic sleep restriction’, which results in sleep loss. It is defined as habitual sleep durations that are less than 7 h, but more than 4 h per night [35]. It may occur due to work, medical conditions or lifestyle [133]. Sleep loss may also result from total sleep

deprivation, such as may occur in shift work, or sleep disruption which can occur in sleep disorders such as restless legs syndrome or sleep apnoea [133].

What Proportion of People Report Short and Long Sleep?

A cross-sectional, population survey conducted in the US (2004–2007 National Health Interview Survey Sample Adult Files) found that 28.3% of adults sleep 6 or fewer hours (chronic sleep restriction), 8.5% sleep 9 or more hours, and only 63.3% sleep 7 or 8 h [80]. In Australia, around 16.6 and 13.9% of middle-aged Australians reported short and long sleep respectively [93].

Factors Associated with Longer and Shorter Sleep Duration

Analysis of the US 2004–2007 National Health Interview Survey Sample Adult Files which provided nationally representative data for 110,441 non-institutionalised US adults aged 18 years or older found the following characteristics were associated with increased odds of both long and short sleep duration:

- being older
- being non-Hispanic black
- being a current or former smoker
- having low levels of education
- having lower levels of income, or few income sources
- consuming few or numerous drinks in a week
- reporting cardiovascular disease, diabetes, depression, underweight, or activity limitations

Additional variables were associated with shorter sleep duration and included living with young children, being unmarried, working long hours and more frequent binge drinking, whereas additional variables associated with longer sleep hours included being younger, being Mexican American, pregnancy and low levels of physical activity [80].

Other cross-sectional survey data found that minority status and lower socioeconomic position were associated with shorter self-reported sleep durations [181].

As a comparison to the US data, in another part of the world totally, Korea, short sleep has found to be associated with older age, lower income level, night or shift work, heavy smoking, depression and anxiety. Long sleep, on the other hand, was associated with younger age, being divorced or widowed, heavy smoking, underweight, depression, anxiety and poorer self-reported health [142].

Health Risks of Poor Sleep

Most people can relate to the feelings of impaired daytime function and fatigue, lack of concentration and memory problems associated with a poor night's sleep. However, when poor sleep becomes chronic, the consequences are far more serious. It has been estimated that sleep disorders could contribute to up to 70% of diseases [143].

Sleep loss causes impairments in cognitive performance, induces sleepiness, fatigue and mood changes, and has been found to reduce performance in simulated driving [133]. Individuals with sleep disorders are more likely to develop a mood disorder and substance abuse [135], and can affect quality of life, increase risk of injury and strain relationships. Lack of sleep is as dangerous as alcohol in relation to driving a car [143]. Research indicates that night shift workers are tripling their chances of developing a mental illness [143].

Interaction of Chronic Insomnia and Other Medical Conditions

Chronic insomnia interacts with other medical conditions. It has been found to be associated with depression [8, 70, 166], anxiety disorders [70], cognitive decline [184], cortical atrophy [156], decreased immune functioning [148], hypertension [8, 15, 49, 177], and other cardiovascular disease [19, 46, 85]. Likewise chronic sleep restriction has been associated with motor vehicle and industrial accidents, hypertension, diabetes, obesity and depression, and increased mortality [60, 64, 93, 94].

Cognitive Functioning

Although there is a general consensus that insufficient sleep leads to slower response speed and greater performance variability for simple measures of alertness, attention and vigilance, there is debate about the effect of lack of sleep on higher order cognitive functions such as perception, memory and executive functions and whether it affects cognitive abilities globally or whether it affects some aspects more specifically [72]. Neuroimaging suggests that the prefrontal cortex may be specifically affected by sleep deprivation, however, executive function tasks measuring prefrontal functioning have not found consistent results. Evidence suggests that some aspects of higher level cortical function remain degraded following sleep deprivation even when alertness and vigilance is restored. There is increasing evidence that lack of sleep may affect cognitive systems that rely on emotional data particularly [72].

In children and adolescents, most studies support the contention that sleep facilitates working memory and memory consolidation. Research indicates that performance in abstract and complex tasks involving higher brain functions decreases more strongly following sleep deprivation than performance in simple memory tasks [77]. Total sleep deprivation has been found to impair attention and working memory, and also affect long-term memory and decision-making, whilst partial sleep deprivation influences attention, particularly vigilance [1].

Cardiovascular Disease and Diabetes

A systematic review found that short duration of sleep was associated with a significantly greater risk of developing or dying of coronary heart disease (Relative Risk RR 1.48), stroke (RR 1.15) but not total cardiovascular disease, and that long duration of sleep was associated with a significantly greater risk of developing or dying of coronary heart disease (RR 1.38), stroke (RR 1.65) and total cardiovascular disease (RR 1.41) [19].

Another study in Chinese adults living in Singapore found that short and long sleep duration was positively associated with coronary heart disease (CHD) mortality. Compared with those sleeping 7 h, the relative risk of CHD death for a sleep duration of 5 h or less was 1.57, whereas for a sleep duration of nine or more hours, it was 1.79 (both statistically significant) [153].

Several studies indicate that shortened sleep increases the risk of having or developing type 2 and impaired glucose tolerance [73, 116, 52]. Poor blood glucose control may cause disruption of the hypothalamic–pituitary–adrenal (HPA) axis and increased consumption of low-quality foods [38], and consumption of low-quality foods can lead to obesity if consumed in high amounts, as well as inflammation within the body.

Interestingly, it is not just getting too little sleep that can be a problem—it is also getting too much of it. The European EGIT-RISC Study found that in men, too little or too much sleep was associated with increased risk of diabetes or impaired glucose metabolism [141]. A similar result was found in the Sleep Heart Health Study which found that a sleep duration of ≤ 6 or ≥ 9 h was associated with increased prevalence of diabetes and impaired glucose tolerance [52]. A prospective, population-based study in Sweden found that falling asleep or regular use of hypnotics was significantly associated with development of diabetes (Odds Ratio 1.52) [116].

Obesity and Sleep Disorders

Obesity is a risk factor for cancer and cardiovascular diseases including diabetes and Metabolic Syndrome. Sleep disorders have been found to be associated with obesity [48, 75, 121]. Studies have shown that:

- Short sleep duration is independently associated with weight gain, particularly in younger age groups [121].
- Durations of sleep under 7 h has been found to be associated with higher body mass index and increased risk of obesity [48].
- People who slept less than 6 h per night regularly were much more likely to have excess body weight compared with those who slept an average of 8 h per night (who had the lowest relative body fat) [75].

The association between chronic sleep deprivation and obesity is likely to be bidirectional, for example obesity can contribute to sleep apnoea which can disturb sleep [94].

There are three potential pathways hypothesised linking chronic sleep restriction and obesity: alteration of neuroendocrine and metabolic pathways and functioning, altered glucose regulation, and altered waking behaviour [94].

Research indicates that when people slept for only two to four hours for two consecutive nights, there was an 18% reduction in leptin and a 28% increase in ghrelin [160]. A reduction in leptin and an increase in ghrelin, in combination, leads to increased appetite. Sleep deprivation can lead to food cravings for sweet and starchy foods especially.

Six nights of restricted sleep in healthy young men was associated with a 30% reduction in glucose effectiveness and a 40% decline in glucose utilisation; glucose tolerance and thyrotropin levels were significantly lower, and evening cortisol levels significantly higher, as were levels of sympathetic nervous system activity, when sleep was restricted compared to the fully rested state [161]. Short sleep, even one night, has been shown to induce insulin resistance which can also lead to weight gain [36] and insulin resistance is a risk factor for development of several types of cancer such as breast, liver, colorectal, pancreatic and lung [5, 17, 124]. Stress can elevate cortisol levels, and elevated levels of cortisol can cause weight gain, weaken the immune system, and increase risk of developing diabetes and osteoporosis [24].

Mood, Anxiety and Depression and Sleep Disorders

Poor sleep can lead to altered mood, anxiety and depression. Chronic sleep restriction has been found to alter mood by compromising psychosocial functioning and negatively affecting an optimistic outlook [53]. Short and long sleep duration have been found to be associated with decreased ability to regulate emotions in a study in women [131].

Insomnia is associated with anxiety and depression [8, 166]. This is very relevant in patients with cancer who often have significant anxiety and depression, as discussed in Chap. 2. For example, insomnia is associated with a 2.6 times greater risk of developing depression in a meta-analysis, and another study found that people with insomnia were 9.8 times more likely to have clinically significant depression and 17.4 times more likely to have clinically significant anxiety [166]. Anxiety and depression have also been implicated in contributing independently to poor outcomes seen in patients with heart failure [75] and have been associated with cardiac events [163].

Mortality and Sleep

A U-shaped relationship between sleep duration and mortality has been found in epidemiologic studies, meaning that both short sleep and longer sleep duration are apparently associated with reduced mortality. The relationship between short sleep duration and diabetes, obesity and hypertension provides plausible evidence for an association between short sleep and reduced mortality, however, the relationship between longer sleep and mortality is not so easily explained.

When multivariate longitudinal analyses of the first National Health and Nutrition Examination Survey were conducted, like other studies they found a U-shaped relationship between sleep duration and mortality. However, when they stratified for age, it was found that there was no association between short or long sleep duration and mortality in middle-aged subjects (32–59 years), and that the U-shaped relationship was only found in the elderly (60–86 years). Thus, the relationship between longer sleep and mortality found in the non-stratified analysis was largely influenced by deaths of elderly subjects and measurement of sleep durations closely prior to death. The researchers concluded that longer sleep duration is unlikely to contribute to mortality and is probably a consequence of medical conditions associated with chronic inflammation and age-related sleep changes [50].

Pain and Sleep

There is a heightened sensitivity to pain with insomnia [158]. Chronic sleep restriction may also contribute to the onset and amplification of pain [53]; a tired body produces chemicals that sensitise the body to pain [140].

Research has demonstrated that patients with sleep problems have significantly more pure musculoskeletal pain than those without sleep problems [2].

Conversely, increased sleep allows the body to tolerate pain better [137]. A good sleep has been shown to be similar to taking 30–60 mg Codeine [138], hence the

importance of ensuring that cancer pain is controlled enough in order to allow sleep to occur, which in turn will help reduce cancer pain.

Sleep and Cancer

The proportion of insomnia in patients with cancer is approximately three times higher than the proportion in the general population [120]. Insomnia affects up to 50% of cancer patients [118, 136]. The prevalence of sleep disturbances in cancer patients ranges between 30% and 75% of newly diagnosed or recently treated cancer patients [42]. It affects 20–70% of newly diagnosed or recently treated breast cancer patients [43].

Sleep disorders are associated with pain, fatigue, depression, anxiety and vasomotor symptoms, depending on comorbidities, treatment and stage of cancer [31]. Commonly reported complaints include difficulty falling asleep, difficulty staying awake, and often, prolonged night-time awakenings [42]. Another common complaint is not feeling rested in the morning [143]. Insomnia can continue long after treatment: symptoms of insomnia have been found in 23–44% of patients 2–5 years after treatment for cancer [39, 169]. Unfortunately, one study found that only 16.6% of patients informed their healthcare practitioner about their insomnia and many practitioners fail to ask about sleep [39].

There are many reasons why sleep may be disturbed in those with cancer including the physical illness itself, pain associated with it, hospitalisation (sleeping in an unfamiliar place, surrounded by noise from others and disruption of doctors or nurses performing routine checks), side effects of drugs and other cancer treatments, and of course, the psychological impact of a diagnosis and living with cancer [143].

Insomnia and sleep disturbances can lead to fatigue, mood disturbance and contribute to immune suppression which affects quality of life and may also impact on the course of the disease [118]. In women with breast cancer, insomnia was significantly associated with worse depressive symptoms and vasomotor symptoms, particularly night sweats [10]. In a study of patients undergoing chemotherapy, those with insomnia had significantly more depression and fatigue than those who slept well [120].

Associations Between Poor Sleep and Individual Cancers

Individual studies have found associations between sleep duration or disruption and individual cancers. For example, disruption and sleep loss has been shown to be associated with an increased risk of prostate cancer [157]. Both longer (≥ 9 h) and shortened (≤ 5 h) durations of sleep have been found to be associated with a higher incidence of colorectal cancer in postmenopausal women [69]. However, a meta-analysis of 10 prospective studies (8392 incident cases and 555,678

participants) did not find a significant association between cancer and shorter or longer sleep duration for most cancers, though they did find that long sleep duration was associated with colorectal cancer [92].

Insomnia and Cancer-Related Fatigue

Insomnia needs to be distinguished from cancer-related fatigue—these two are different, however, they are related as insomnia can lead to daytime fatigue which can impact adversely on functioning, and fatigue can lead patients to nap during the day, thereby interfering with sleep at night [118].

Insomnia and Cancer Pathogenesis

How poor sleep affects the body at the cellular level is understandably complex. For example, insomnia releases chemicals that can promote inflammation, which is associated with cancer and most chronic illness [68]. Loss of sleep has been found to induce a functional alteration of the monocyte proinflammatory response and the molecular processes driving cellular immune activation and inducing inflammatory cytokines. Loss of sleep induced significantly greater monocyte production of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) and a threefold increase in transcription of interleukin messenger RNA and a twofold increase in TNF-α messenger RNA [68]. Poor sleep has also been found to be associated with increased sympathetic nervous system activity as measured by 24-h urinary catecholamine levels, which is postulated as a possible link between poor sleep and cardiovascular and metabolic complications [190].

Interleukin-6

Research suggests that sleep is involved in the nocturnal regulation of Interleukin (IL)-6 as well as Growth Hormone, whereas melatonin and cortisol are believed to be circadian-driven hormones [132]. When the sleep of healthy young male and female adults was restricted to 6 h per night, the 24-h secretory profile of interleukin (IL)-6 was increased (both men and women) and TNF-alpha was increased in men [173]. These are both markers of systemic inflammation.

Another study evaluated the effects of nocturnal sleep and partial night sleep deprivation (kept awake until 3 a.m.) on circulating levels of IL-6 in 31 healthy men. Sleep onset was associated with an increase in serum levels of IL-6 under normal sleep conditions, and when sleep was delayed until 3:00 a.m., the nocturnal increase in IL-6 was also delayed until then. The nocturnal increase in IL-6 occurred in

association with stage 1–2 sleep and REM sleep. Levels during slow wave sleep were the same as those while awake. Growth hormone followed a similar pattern to IL-6 (whilst melatonin and cortisol showed no concordance with sleep). IL-6, though pro-inflammatory, plays an important part in the function and regulation of peripheral blood mononuclear cells of the immune system (it is also thought to have somnogenic effects, having low circulating levels during the day and high levels at night, and can stimulate the HPA axis). Sleep deprivation has been found to lead to oversecretion of IL-6 during the day and undersecretion at night [174]. Therefore, loss of sleep may decrease nocturnal IL-6 levels, which could negatively impact on the immune system functioning [132]. Another possibility, though, is that in depressed or aged populations who generally show increased amounts of REM sleep and a relative loss of slow wave sleep, there may be elevation in nocturnal concentrations of IL-6 and this could contribute to inflammation [132]. Inflammation underpins most chronic diseases including cancer.

Tumor Growth and Poor Sleep

Research in animals gives us a few more insights into what might be occurring in humans when sleep is poor. Research in mice models has demonstrated that poor quality sleep such as sleep characterised by frequent awakenings can speed the growth of cancer, increase tumor aggressiveness and depress immunity [54]. In sleep-deprived mice, tumor-associated macrophages (TAMs) were more numerous and distributed closer to the tumor capsule compared with control mice. TAMs contribute to cancer progression by releasing many different chemicals including growth factors, cytokines, inflammatory mediators and proteolytic enzymes which are involved in tumor growth and invasion [54].

Genes and Sleep Deprivation

Sleep deprivation has been found to affect hundreds of genes related to circadian rhythms, metabolism, inflammation, immune response and stress [105]. In a study conducted in humans, in response to insufficient sleep 711 genes were up- or downregulated, the number of genes with a circadian expression profile was reduced and the number of genes responding to total sleep deprivation increased from 122 to 856. Genes affected by insufficient sleep were associated with circadian rhythms, sleep homeostasis, oxidative stress, and metabolism. Sleep deprivation in humans affected several biological processes including chromatin modification, gene expression regulation, macromolecular metabolism, and inflammatory, immune and stress responses. Such processes may be involved in the health problems or illnesses found to be associated with sleep deprivation [105].

Cortisol and Poor Sleep

Cortisol is another hormone that has far-reaching effects on the body and plays a role in the stress response, as discussed in Chap. 2. A sign of dysregulation of the HPA axis and endocrine stress response is alterations to the circadian cortisol rhythms. Cortisol levels are usually highest just before awakening and decrease during the day in healthy individuals, but in women with advanced breast cancer, up to 70% show flattened circadian profiles, indicating consistently high cortisol levels or erratic fluctuations [14, 171].

Cortisol dysregulation has been linked with both the physical and psychological stresses of cancer [25, 108]. A study in women with metastatic breast cancer found that a flatter diurnal cortisol slope (indicating a lack of normal diurnal variation) was a significant predictor of shorter survival time. The study also found that patients with flatter cortisol slopes had lower NK cell counts and suppressed NK cell activity, and that patients who reported more nocturnal awakenings had flatter cortisol slopes [152].

Sleep research has found that cortisol secretion is elevated the evening following partial or total sleep deprivation in normal, healthy young men. Normally, following the early morning circadian elevation of cortisol, cortisol levels decline over the day. However, they found that following sleep deprivation, this decline occurred at a slower rate, implicating alteration of the hypothalamic pituitary adrenal (HPA) axis. Sleep loss, it was concluded, is not so much an acute stimulus or stressor for the HPA axis as something that affects the resiliency of the HPA 'response to endogenous stimulation by circadian rhythmicity' [89].

Cortisol regulation is important as animal and in vitro research has demonstrated that glucocorticoids are involved in tumor growth [91, 144], with cortisol accelerating tumor growth either by suppressing the immune system or affecting metabolic processes [139]. Altered cortisol rhythms found in women with metastatic breast cancer are associated with disrupted patterns of circulating leukocytes, neutrophils, platelets and serum proteins [152, 167].

Mechanisms for a Circadian Disruption Model of Cancer

When one considers what the circadian rhythm controls, there are several biologically plausible mechanisms for a circadian disruption model of cancer. Circadian rhythms control several physiological processes including sleep/wake cycles, hormone levels, body temperature, metabolism and the immune system [154].

Melatonin plays a critical role in free radical scavenging and energy balance, has an anti-proliferative effect, particularly in oestrogen receptor ER+ breast cancer cells, and exposure to electric light and electromagnetic waves can interfere with its production and secretion [154]. Both breast and colon cancers are linked to circadian disruption; epidemiological studies have found correlations with regions where circadian disruption is prevalent, as well as in night shift workers, lending

further support for a role of circadian disruption in carcinogenesis [154]. For example, several studies have found a clear association between night shift work and incidence of breast cancer [55, 100, 150] as well as colorectal cancer [151].

A Complex Picture at the Cellular Level

These research findings paint just some of the picture of what happens at the cellular level when there is poor sleep and how sleep deprivation may contribute to carcinogenesis. Lack of sleep is a significant cause of stress, and the way in which ongoing stress can mediate changes in physiological functioning via a range of factors including other hormones such as prolactin and oxytocin that can promote tumor growth is immensely complex. We have only scratched the surface in this brief description. The reduction of stress is such an important factor in the management of cancer.

There are several factors that are part of modern life that may also be contributing factors to carcinogenesis, or at the very least, disrupters of sleep via their impact on circadian rhythms, as discussed in the next sections. These include the electric light, electromagnetic waves and the advent of shift work.

Electric Light, Disrupted Circadian Rhythms, Poor Sleep and Cancer

Over millions of years, humans and other forms of life have evolved an endogenous circadian rhythmicity or biological clock in which there are daily oscillations in physiology that allow for anticipation of sunrise and sunset [162]. Circadian rhythms synchronise the body functions with the environment, synching the body functions with the level of diurnal and nocturnal activity [154, 162], regulating hormones, core body temperature, and cell growth, division and metabolism [61]. The markers of the phases of the circadian rhythm are core body temperature and plasma levels of melatonin and cortisol [30].

Circadian rhythms are entrainable and can be reset by external stimuli, e.g. light [154]. The 24-h physiological rhythmicity is normally controlled by the daily cycle of light and dark, however, with the introduction of the electric light, this has caused interference with this natural cycle: with artificial light there is too much light at night for a true dark to be detected, and inadequate light inside during the day for a resetting of the endogenous circadian rhythmicity [162]. Consequently, the circadian rhythm is disrupted, causing disturbances to the sleep/wake cycle, as well as other body functions including hormone regulation and gene expression [162]. Melatonin is entrained by light cues, so when the body is exposed to light at inappropriate times (for example, at night when we turn on our houselights), melatonin can be suppressed when it would normally be released [6].

Electric lighting may play a causative role in several diseases via suppression of melatonin, circadian gene expression, and a link between circadian rhythmicity and metabolism [162]. Disruption of circadian rhythms may be involved in the development of cancer, as well as Metabolic Syndrome, diabetes (both risk factors for cancer) and other cardiovascular disease [154]. Disruption of the circadian rhythm and exposure to light at night has been linked to an increased risk of breast cancer [58], for example.

Electromagnetic Waves and Disrupted Circadian Rhythms

In addition to exposure to artificial light, exposure to electromagnetic waves from power lines and electrical appliances have been found to disrupt circadian rhythms [154]. Exposure to variable intensities of EM waves on a regular basis can interfere with the production and secretion of melatonin [16]. Computer screen emission intensity is high at those wavelengths of light where melatonin is most readily suppressed (464–484 nm), so excessive computer use, particularly at 'non-circadian' times may also disrupt circadian rhythm [154]. Animal models have found that exposure to low-frequency EM can suppress melatonin levels at night [16].

Growing Evidence that Use of Cell Phones May Cause Cancer

More disturbingly, though, exposure to high-frequency electromagnetic waves can interfere with brain activity [78] and animal research has demonstrated that low-level radio frequency radiation exposure can cause DNA modification [84].

The World Health Organization [183] reports that:

> The electromagnetic fields produced by mobile phones are classified by the International Agency for Research on Cancer as possibly carcinogenic to humans

The International Agency for Research on Cancer (IARC) evaluation of mobile phone use was primarily based on data from the IARC study and the Hardell group in Sweden, and data from both demonstrated an association between two types of brain cancer, glioma and acoustic neuroma, and exposure to radiofrequency electromagnetic fields [56].

Danish Statistics Indicate an Increase in CNS Tumors with Mobile Phone Use

Despite claims from various governments, for example the Swedish Radiation Authority's 2016 report which stated that '*cancer rates in Sweden and other*

countries do not show any increase that might be attributed to the massive mobile phone use that started in the beginning of this century', there is growing evidence that this may not be accurate. A report from the Swedish Radiation Foundation Protection Agency stated that brain tumors in the Swedish Cancer Registry are underreported, and that data from the Danish Cancer Registry indicates that number of people diagnosed with central nervous system tumors (including brain tumors) in Denmark has more than doubled since 1990 (827 new cases in 1990 to 1807 in 2015) [164]. It also states that tumors of the central nervous system are the type of cancer that has increased the most in young people aged 0–39 years [164].

Evidence of an Association Between Long-Term Wireless Device Use and Malignant Brain Tumors

Case control studies have confirmed an association between long-term mobile and cordless phone use with malignant brain tumors, providing support for a causative role of radiofrequency electromagnetic fields (EMFs) in initiation and promotion of carcinogenesis, including glioma acoustic neuroma and meningioma [28, 56, 67, 146], although at least one study did not support an association with acoustic neuroma [125]. For example, one study found support for an early effect (initiation) in carcinogenesis by analogue phones and a late effect (promotion of carcinogenesis) with digital wireless phones. They found that in general, odds ratios of malignant brain tumors increased with increased latency (time from first use) for all wireless phones (included analogue, 2G, 3G, cordless phones), and that the highest odds ratios were found in those who had higher phone usage [56]. For >1 year latency, the Odds Ratio was 1.7 (95% Confidence Interval 1.04–2.8) which increased to 2.6 for latency period of >1–5 years, decreased again with increased latency in the intervening latency periods (>5–10 years and >10–15 years), then increased to 3.0 (95% Confidence Interval 1.5–6.0) for latency >25 years [56]. Ipsilateral phone use was associated with a higher risk of a brain tumor on the same side as the mobile and cordless phone use than for contralateral use [56].

Microwave Radiation Exposure Modelling

Modelling of mobile/cell phone radiation absorption in the head shows that microwave radiation can extend into the brain and eye in adults and that there is even greater absorption in children's brains (temporal and frontal lobes, extending into brainstem) and eyes and cheeks [33]. When a mobile phone is placed in the pocket, modelling demonstrates that the bone marrow and reproductive organs are exposed to microwave radiation. Similarly, when a cell phone is placed in a woman's bra, it exposes the breast tissue to this radiation [33]. The cumulative impact is what is what is likely to be dangerous. Case reports have demonstrated,

for example, that breast tumors have developed directly under the area where a cell phone has been kept habitually [33, 178]. Researcher Davis advises that tablets and other devices are tested 20 cm away from the body—they are not approved to be held in the laps of children, despite the fact that tablets are now very commonly used in schools [33].

Action of Some Schools and Libraries

Some schools and libraries in the US are getting rid of WiFi and instead using cable for internet connectivity as a response to concerns about EMFs [44]. Readers are referred to other sources of information on potential health risks of electromagnetic radiation such as Donna Fisher's 'Dirty Electricity and Electromagnetic Radiation' [44], which although not written for a scientific audience, provides some rather sobering information nonetheless that we may be seriously putting our health at risk.

Tips for Reducing Exposure to Mobile/Cell Phone Electromagnetic Waves [33, 44]

- Don't carry your mobile phone/cell phone on your body, e.g. in your pocket or for women, in your bra
- Don't hold the mobile phone/cell phone next to your head or against any other part of the body when in use
- Only use mobile phones/cell phones for very short voice calls
- Use the mobile phone/cell phone on 'speaker' mode or use an 'air tube' headset
- Avoid having the mobile phone/cell phone (or tablet) in your bedroom and turn it off at night
- Avoid using your mobile phone/cell phone in cars, trains, buses or elevators
- Put the mobile phone/cell phone on 'airplane mode' when not in use

Shift Work, Sleep and Cancer

Shift work has been labelled a carcinogen [31]. The internal biological clock adapts slowly, or not at all, to rapid transitions between shift work schedules. Misalignment of rhythmic physiological systems occur, such as sleep, metabolism, alertness, performance, melatonin and cortisol, leading to sleep deprivation and poor performance. There are clock gene variants that may influence tolerance of

sleep deprivation. Those who engage in shift work have a higher risk of cancer and heart disease which may be partly due to the frequent circadian desynchrony. Light at night, melatonin suppression and circadian desynchrony have been implicated in certain cancers [6].

Studies in pilots and night shift workers, both of whom have disrupted circadian rhythms, have shown an increased risk of cancer, particularly prostate cancer [9, 26, 32, 81, 129]. The link between prostate cancer and melatonin comes from observations that men with prostate cancer have lower levels of circulating melatonin, the finding that melatonin has oncostatic properties in prostate cells (melatonin has also been found to be oncostatic in colon cells), and its inverse effect on circulating levels of other androgens [154]. Environmental influences that affect melatonin therefore may play a role in prostate cancer [154]. There is a greater incidence of endometrial cancer [176], and Non-Hodgkins Lymphoma [86] in night shift workers also. Systematic reviews have found weak evidence of a link between increased breast cancer incidence and shift work [66, 71], in particular flight attendants flying internationally or overnight and nurses working night shift [71].

The story, of course is more complex. Readers are referred to other sources [6, 154] for a more comprehensive understanding of the physiological impact of poor sleep and its potential role in cancer.

Integrating Strategies for Better Sleep into a Wellness Plan

The use of sleep medications is rapidly increasing—almost 10 million prescriptions are written annually in Australia for sleep medications. These can be useful as short-term aids, but it is more beneficial to review lifestyle causes and make the necessary adjustments. The Integrative Medicine model provides us with a range of sleep-promoting interventions that deal specifically with causes rather than symptoms and can also be beneficial to overall health and wellbeing.

There are several strategies that may be incorporated into a Wellness Plan to assist cancer patients achieving a better night's sleep, where sleep is poor. These include:

- General sleep hygiene guidelines
- Diet
- Posture
- Exercise
- Relaxation/Meditation/Yoga
- Cognitive Behavioural Therapy
- Sunshine and bright light therapy
- Supplements that may enhance sleep, including western herbs
- Homoeopathy
- Chinese medicine including Chinese herbal medicine and acupuncture

These will be discussed in the next sections. It should be noted, however, that in general, there are few randomised controlled trials in cancer-related sleep disorders, so the most recommendations tend to be based on treatment of primary insomnia [31].

Before discussing such topics with the patient, an assessment of sleep patterns should be conducted in order to understand the nature of the sleep problem. Also, it is important to assess what medications the patient may be taking, since many drugs can interfere with sleep.

Assessment of Sleep

It is important to establish the history of the disturbance to sleep, for example, has the patient always had sleep problems from childhood or was it triggered by a stressful event. The clinician will need to understand the nature of the patient's sleep pattern, for example does the patient have difficulty going off to sleep (which is usually associated with stress) or do they wake in the early hours (usually associated with depressed mood) or do they have disturbed sleep and once awake, have difficulty falling asleep again?

Understanding the patient's natural body clock is also important—delayed sleep phase disorder is commonly undiagnosed. In this disorder, the person's natural rhythm is to fall asleep later than usual (typically after midnight), they generally sleep well after falling asleep, and their natural wake time is much later than for most people. However, this rhythm is often incompatible with normal work start times [29].

The clinician should also check for any triggers or contributing factors: these can include consuming drinks containing caffeine or drinking alcohol at night, exercising late at night, and eating spicy foods [29]. Sleeping with a partner who snores or tosses and turns in bed, or is a shift worker who may come home after the patient has gone to bed are also factors that might contribute to poor sleep.

How the poor sleep is impacting on the patients and how they are coping is critical to understand, given the relationship between insomnia and anxiety and depression which can reinforce each other. For example, common daytime consequences of poor sleep include changes in mood, irritability, poor memory, fatigue, low energy and general malaise and can lead to absenteeism from work [29].

The clinician also needs to be aware of potential co-morbid conditions that may be contributing to the insomnia or poor sleep. For example, men over the age of 50 may develop symptoms of benign hyperplasia of the prostate, and if this is causing them to have to get up to urinate two or three times per night, this can have a significant impact on sleep.

Finally, many patients have already tried various things to alleviate their insomnia, so clinicians should check with them to see what they might already have tried and whether they had any success or not.

Sleep Checklist

There are some validated questionnaires such as the Auckland Sleep Questionnaire [7] which can assist in identifying sleep disorders, and the Insomnia Severity Index [107] which can document severity of symptoms and chart response to treatment [29]. The clinician can also suggest that the patient complete a two week sleep diary (there are several available online) in order to gain better insight into sleep patterns. Actigraphy using a wrist monitor to record sleep-wake cycles can be used to objectively measure sleep [29].

Table 4.1 sets out a short checklist of questions that may be useful for the clinician to use during their consultation.

Assessment of Medication

A major cause of sleep disorders can be western pharmaceuticals. Drugs are known to interrupt REM sleep cycles and while it may be necessary to use medication to relieve pain symptoms that interfere with sleep, this can often create a counter-productive cycle. Alternative pain relief strategies can be explored. Prescription drugs that may cause sleep problems include: beta blockers, ACE inhibitors, antidepressants, anti-anxiety drugs, corticosteroids (including prednisolone), levo-dopa (anti-Parkinsonian), cough and cold preparations, thyroid hormones and others [143].

Table 4.1 Sleep checklist of questions

	Sample questions	Response/Notes
History of sleep problem	When did the sleep problem (e.g. insomnia) first manifest? (e.g. as a child or as an adult, or related to a particular medical problem, e.g. cancer?) What if there is a particular event that occurred, after which the insomnia began? Was it related to a period of stress, anxiety or depression? How long have you had difficulty sleeping?	
Nature of sleep pattern	How long do you sleep for? What time do you go to bed? How long does it take for you to fall asleep? What time do you wake up? When you wake up do you feel refreshed or tired? Do you wake during the night? If you wake during the night, do you fall back to sleep easily? Do you need to get up to the toilet to urinate at night? If so, how many times?	

(continued)

Table 4.1 (continued)

	Sample questions	Response/Notes
Triggers or contributing factors	Do you notice that if you do particular activities or eat particular foods, you are more likely to have a poor night's sleep? Do you drink coffee or tea? If so, how many cups per day? When is the last cup that you drink? Do you drink energy drinks? If so, how many per day and at what times during the day would you drink these? Do you read or watch television in bed? Do you read emails or surf the internet on a tablet, laptop or phone in bed? Do you have animals that sleep with you either in the bed or in the bedroom? Do you drink alcohol and if so, how many standard drinks per day would you have and at what time of day would you have them? Do you smoke? If so, how many cigarettes per day? What time is the last cigarette of the day typically?	
Alleviating factors or strategies	Is there anything that you have tried that seems to contribute to a better night's sleep?	
Impact on life	How is the poor sleep impacting on you? How does poor sleep affect your general mood? How does it affect your ability to function at work? Does it have any effect on driving or other activities that you might need to do as part of your work, and if so, what are these?	
Comorbid conditions that may contribute to insomnia	Clinician to record as part of patient history	

Sleep Hygiene

Tips for getting a better night's sleep commonly focus on getting to bed earlier, changing bedroom conditions (temperature, darkness, noise), avoiding stimulants such as caffeine and alcohol, maintaining regular sleep times and managing stress. These are all important components of 'sleep hygiene'.

Computers, tablets and mobile phones should be left out of the bedroom. Apart from the potential effects that exposure to electromagnetic frequencies might have on the brain, anything that stimulates the mind like surfing the net is not likely to be conducive to sleep. The habit of checking emails, in particular work-related emails late at night is another modern phenomenon that interferes with allowing the mind and body to relax. Phones are best left out of the bedroom.

The US National Sleep Foundation has many useful ideas about good sleep hygiene including how to set up a bedroom, positions for sleeping, etc., that may assist. These include:

- Sticking to a sleep schedule: same bed time and same wake-up time
- Practising a relaxing bedtime ritual
- Eliminating daytime cat-naps
- Exercising daily
- Designing a sleep environment conducive to sleep including a cool temperature, free from noise, free from light and free from other distractions
- Sleeping on a comfortable mattress and pillows [110]

Diet and Sleep

Diet can play an important role in sleep. Many of the brain chemicals necessary for good sleep can be found in specific foods. If intake is problematic there is also the possibility of obtaining these essentials in supplement form, under the guidance of an integrative medical practitioner or other health professional. Conversely there are foods that contain substances that can interfere with sleep.

Table 4.2 sets out foods that may enhance sleep which may be integrated into a Wellness Plan. Table 4.3 sets out foods that may contribute to poor sleep.

Table 4.2 Foods that enhance sleep

Food	Mechanism of action
Cherries	Contain melatonin, the chemical that helps control our body's internal clock
Milk	Contains the amino acid tryptophan, a precursor to the brain chemical serotonin that promotes relaxation and sleep
Complex carbohydrates such as quinoa, barley, buckwheat and whole-wheat bread	These are, in general good for sleep but it is not a great idea to binge on carbohydrates before bedtime
Banana	Contains the natural muscle relaxants magnesium and potassium Also a source of carbohydrates
Turkey	Contains tryptophan, a chemical that can make people feel sleepy
Other sources of tryptophan: hummus, lentils, eggs, milk, proteins and many nuts and seeds	Contain tryptophan, a chemical that can make people feel sleepy
Sweet potatoes	Provide sleep-promoting complex carbohydrates, and the muscle-relaxant potassium

Based on data from Samvat and Osiecki [143]

Table 4.3 Foods that may adversely affect sleep

Food	How it adversely affects sleep
Cheeseburgers	Very high fat content. Fat stimulates the production of stomach acid which can cause oesophageal reflux (heartburn)
Alcohol, including wine [143]	Metabolises quickly and can cause person to wake multiple times during the night (reduces REM sleep, and in long-term users can cause difficulty falling asleep). Also increases propensity to snore
Coffee and teas [143]	Contains caffeine, a central nervous system stimulant
Energy drinks	Very high in caffeine. They are best avoided later in the day or, even better, avoided completely
Soft drink	Contains high amounts of sugar, caffeine and the preservative sodium benzoate and other chemicals that can aggravate the gastrointestinal tract and promote acid reflux
Heavily spiced foods	Can keep people awake at night, especially if the spices contribute to heartburn

Posture and Sleep

Many patients who are overweight suffer from sleep disordered breathing [188]. Population studies have shown an increase in prevalence with increased body mass index and neck girth, and clinical studies of weight loss support a causal association [188]. Changes in posture during sleep have been found to improve sleep apnoea. In severely affected patients with obstructive sleep apnoea, upper body elevation and to a smaller extent, lateral positioning, have been found to significantly improve upper airway stability during sleep [114].

Exercise and Sleep Promotion

Many studies show exercise promotes better sleep. Regular physical exercise may promote relaxation and raise core body temperature in ways that are beneficial to initiating and maintaining sleep.

The US National Sleep Foundation's [111] Sleep in America Poll: Exercise and Sleep provides a very detailed summary of the benefits of exercise in relation to sleep promotion. In this survey of 1000 people, participants were subcategorised into four activity levels: vigorous (activities that require hard physical effort, e.g. running, cycling, swimming, competitive sports), moderate (activities that require more effort than normal, e.g. yoga, tai chi, weight lifting), light activity (walking) and no activity. The results clearly demonstrated the positive benefits of exercise, in particular, vigorous exercise [111]. Key findings are set out in Table 4.4.

A meta-analysis of 66 studies found that acute exercise has small beneficial effects on total sleep time, sleep onset latency, sleep efficacy, stage 1 sleep and slow wave sleep. It also has a moderately beneficial effect on wake time after sleep onset. Regular exercise was found to have a moderately beneficial effect on sleep quality,

Table 4.4 Key findings of the US National Sleep Foundation's [111] sleep in America Poll: exercise and sleep

• The percentage of those who exercise vigorously, moderately or lightly who report either very good of fairly good overall sleep quality was 83%, 77% and 76% respectively, whilst only 56% of non-exercisers report very good or fairly good sleep quality
• The average amount of hours slept during a week day was similar across all four categories (and was just under 7 h)
• Exercisers were significantly more likely than non-exercisers to report that their sleep needs are being met on workdays (vigorous 70%, moderate 69% and light 68% vs. no activity 53%)
• Exercisers were significantly more likely to perceive their quality of sleep to be better on days they exercise compared with non-exercisers (vigorous 62%, moderate 54% and light 49% vs. no activity 28%), and regardless of exercise level, around half perceive that their quality of sleep improves on the days they exercise
• Vigorous exercisers report the best sleep: they report the largest proportion of very good sleep quality and report the largest proportion of satisfaction with the amount of sleep they actually get compared to the amount of sleep they report needing
• Overall vigorous exercisers had fewer sleep problems (waking during the night, waking up feeling unrefreshed, difficulty falling asleep, waking up early and having difficulty getting back to sleep) in the past two weeks than the other subcategories. The proportion of non-exercisers reporting the first three of these aforelisted sleep problems was significantly greater than the proportion of vigorous exercisers
• The proportion of vigorous exercisers (50%) reporting no problem with maintaining enthusiasm to get things done was significantly greater than the other subcategories
• Vigorous exercises reported a significantly shorter average time to fall asleep (14.7 min) compared with non-exercisers (26.1 min), light exercisers (22.4 min) and moderate exercisers (20.4 min)
• The proportion of non-exercisers who report very bad sleep quality (14%) is significantly greater than vigorous exercisers (3%), moderate exercisers (4%) and light exercisers (4%)
• The proportion of non-exercisers who report poor health (12%) is significantly larger than vigorous exercisers (1%), moderate exercisers (1%) and light exercisers (2%) [111]

Based on data from National Sleep Foundation [111]

small–medium beneficial effects on sleep onset latency, and a small beneficial effect on total sleep time and sleep efficiency. Effects were moderated by several factors including gender, age, baseline physical activity, exercise type, time of day, duration and adherence but were not moderated by exercise intensity or aerobic versus anaerobic subcategorisation [79].

Exercise and Sleep Apnoea

Sleep apnoea is a condition that can affect people who are overweight or obese, and people with cancer are often overweight/obese. A meta-analysis found that exercise has a beneficial effect in reducing the severity of sleep apnoea in patients with obstructive sleep apnoea. There were also significant improvements in cardiorespiratory fitness, daytime sleepiness and sleep efficiency [65].

Relaxation, Meditation and Yoga

Relaxation techniques can be useful when stress and worry causes sleep disruptions. In a recent study, mindfulness mediation had significant benefits for improving quality of sleep. A randomised controlled trial conducted over 6 weeks compared a mindfulness awareness practices (MAPs) intervention with sleep hygiene education (SHE) (both 2 h per week with assigned homework) in adults with moderate sleep disturbances. The MAPs group showed a significant improvement compared to the SHE group in relation to the Pittsburgh Sleep Quality Index and secondary health outcomes of insomnia symptoms, depression symptoms, fatigue severity and fatigue interference. There was no significant difference between groups for anxiety, stress or NF-κB concentration, although the study did find that concentration of NF-κB significantly declined in both groups [13].

Good sleep and meditation both have positive benefits for the optimal functioning of mind and body but there is a difference: in sleep the human mind–body is like a parked car with the engine on, whereas in meditation, the engine has been switched off.

The benefits of various forms of relaxation techniques have been discussed in Chap. 2 in relation to stress. Dealing with the underlying causes of stress where possible, as with cognitive behavioural therapy, is also advisable.

Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy (CBT) is generally the first line therapy for insomnia treatment [96, 134] and research indicates that it can be more effective than sleeping medication for chronic insomnia [103].

Cognitive behavioural therapy for insomnia (CBT-I) is a structured programme, often comprising several techniques, that helps people with sleep disorders identify and replace beliefs, thoughts and behaviours that can contribute to poor sleep with habits that promote good sleep [96]. It helps people get rid of negative thoughts and worries that keep them awake and aims to replace sleep anxiety with positive thinking that links being in bed with sleeping [96, 112].

According to the Mayo Clinic, some of the CBT-I techniques include:

- Sleep hygiene: changing lifestyle habits that influence sleep, e.g. not exercising regularly, smoking, drinking caffeine late in the day, etc., and learning to wind down an hour or two before going to bed.
- Creating a good sleep environment: this can include keeping the bedroom quiet, cool and dark, eliminating distractions such as televisions and computers/tablets/laptops/cell phones in the bedroom, hiding the clock from view.
- Stimulus control therapy: removes factors that condition your mind to resist sleep. Examples: the bedroom is only used to sleep and sex (and not reading emails or doing work); leaving the bedroom if you can't fall asleep within 20 min and returning when sleepy.
- Sleep restriction: involves reducing the time spent in bed, causing partial sleep deprivation and therefore making the person more tired the next night. Once sleep improves, time in bed is gradually increased.
- Relaxation training: including meditation, muscle relaxation, imagery.
- Remaining passively awake (paradoxical intention): involves avoiding any effort to fall asleep and letting go of the worry that you can't sleep (since worrying that you can't sleep can keep you awake).
- Biofeedback: observing biological signs like heart rate, breathing and muscle tension then adjusting them (often uses a biofeedback device to record patterns and help identify those that affect sleep) [96].

CBT-I may also involve talking with a therapist either alone or in a group about thoughts and feelings about sleep, with the goal to settle the mind down [112]. Often several techniques are used together. Working with a therapist who can create an individualised treatment plan would be advisable. Again, the integrated model of care, where there is a team of professional healthcare providers is a most valuable one.

Research Evidence in Support of CBT for Insomnia

There is much research in support of CBT in the treatment of insomnia. For example, a randomised controlled trial (RCT) investigated the efficacy of five sessions of group CBT compared to 'treatment as usual' for insomnia delivered by mental health practitioners. The study found that the group CBT participants had significantly better sleep efficiency post-treatment than those who had usual care (though the difference was smaller between the groups at a 20-week follow-up), but there was no difference between the groups in terms of anxiety or depression symptoms [18]. This study was not specifically in cancer patients, however the results are still relevant and noteworthy.

A systematic review of five studies that investigated the efficacy of CBT in the treatment of insomnia found low to moderate grade evidence that CBT for insomnia is superior to benzodiazepines and non-benzodiazepine drugs in the long term and that its effects may be more durable than medications [103].

Other studies of CBT have been conducted in cancer survivors. For example, an RCT of CBT in breast cancer survivors found that those who received this therapy had significantly better sleep indices, lower levels of depression and anxiety, a lower frequency of medicated nights and a great quality of life compared with the control group (wait list), and that the therapeutic effects were maintained up to 12 months' post-therapy [149]. Other studies in breast cancer survivors have also found significant benefits of CBT in treating sleep disorders [40, 130].

Sunshine and Bright Light Therapy

Where poor sleep is experienced by the patient with cancer, a suggestion can be to increase daytime exposure to the sun (which will also improve vitamin D levels) and reduce exposure to bright lights in the evening. This includes exposure to televisions, computer screens, smart phones and artificial light. This may help to 'reboot' the circadian rhythms and melatonin production in the body.

The use of computers, particularly at night, may lead to circadian disruption [154]. Computer use should be limited in the evening, and these, along with tablets, cell phones and laptops switched off a few hours before bedtime. They should also be left out of the bedroom, in particular in light of evidence that electromagnetic waves from mobile phones can affect the electrical activity of the brain [154], and the potential link between electromagnetic waves and cancer [44]. A study of children born in England and Wales found that compared with those who lived more than 600 m from a high voltage powerline at birth, children who lived within 200 m had a significantly higher risk of leukaemia [37]. Other studies have not found this association [123]. However, there is enough evidence beginning to form to sound a very large cautionary bell. This may well be the next health epidemic that currently no one wants to admit to, not unlike smoking in the twentieth century. In the meantime, why take chances? For patients with cancer, particularly brain cancer, it would be prudent to not hold cell phones against the head nor carry them on the body.

Supplements that Can Enhance Sleep

There are three key supplements that may be prescribed to enhance sleep. These are set out in Table 4.5.

Table 4.5 Supplements that may enhance sleep

Supplement	Note: dosages may vary with individuals
Melatonin	Melatonin is a hormone made in the pineal gland in the brain, produced from the amino acid tryptophan Recommended dosage: 3 mg *at night*
L-tryptophan	L-tryptophan is a precursor to melatonin that is necessary for the body to produce both melatonin and serotonin Recommended dosage: 1 gm *at night*
Magnesium	Helpful if restless legs syndrome is adversely affecting sleep Recommended dosage: 360–600 mg *at night*

Western Herbal Medicines

There are several western herbs that have beneficial actions where sleep is disturbed. Some of these are discussed in the next few pages.

Valerian and Hops

Extracts of the roots of valerian (*Valeriana officinalis*) and hops have both shown efficacy for the treatment of insomnia. Hops is well known as a bitter agent in the brewing industry and has a long history of use for sleep disorders. Valerian is proven to improve sleep quality without any other side effects. Taken together valerian and hops may be even more effective.

A systematic review of 16 randomised controlled trials examining 1093 patients found evidence that valerian improves sleep quality without producing adverse side effects. A dichotomous outcome of sleep quality—improved or not—was reported in six studies, and the pooled results indicated a significant benefit (Relative Risk of Improved Sleep was 1.8, meaning that those who took valerian were almost twice as likely to have improved sleep). However, like many systematic reviews, the review found evidence of publication bias and methodological problems in many of the studies. Despite this, the outcome of the review was favourable towards valerian's use in insomnia [11]. Another meta-analysis of 18 RCTs concluded that valerian is effective in terms of subjective improvement of insomnia (sleep quality improvement) though its effectiveness has not been demonstrated with quantitative or objective measures [41].

Evidence suggests that the combination of valerian and hops may be more effective than placebo or valerian alone. An RCT of a fixed valerian hops extract combination (Ze 91019) was compared with a fixed single extract of valerian (similar amount as in the combination) and a placebo over four weeks in people suffering from non-organic insomnia. The study found that the combination extract (valerian plus hops) was significantly better than placebo whilst there was no significant difference between the single valerian extract and placebo in reducing sleep latency [74].

A very small study in children with intellectual deficits has also found that valerian over 8 weeks was associated with significant improvement in sleep (including increased total sleep time and improved sleep quality and reduced nocturnal wake time and reduced sleep latencies), in particular in children with deficits that involved hyperactivity [47].

Cautions

Since it has a sedative action, there are some cautions: in some people it may cause drowsiness, so caution should be taken if operating heavy machinery or driving a motor vehicle or any other activities requiring mental alertness within 2 h of consumption, and it should not be consumed with alcohol [59]. The usual precautions apply as for any form of herbal medicine—its potential for interactions with western medication should be checked.

*St John's Wort (*Hypericum perforatum*)*

St John's Wort has a long history of assisting patients with depression, and may be useful to assist those patients with sleep problems who also suffer from depression. As stated previously in this chapter, insomnia is associated with anxiety and depression [8, 166]. There is limited data on the efficacy of St John's Wort in the treatment of insomnia that is not related to depression [101].

A systematic review of 29 studies in 5489 patients with depression that compared extracts of St John's Wort to placebo or standard antidepressants over 4–12 weeks concluded that the St John's Wort extract was superior to placebo, similar in efficacy to antidepressants and had fewer side effects than standard antidepressants [90].

St John's Wort has been found to significantly increase the latency to rapid eye movement (REM) sleep without any other effects of sleep architecture [155].

Chamomile

Chamomile has a sedative action and has a history of use in the treatment of insomnia. German chamomile (*Matricaria recutita*) is widely used as a herbal product for sleep, and preclinical studies indicate that the flavonoid constituent apigenin produces sedative effects via its ability to modulate y-aminobutryic acid (GABA) receptors [175, 189, 191].

There has not been a lot of research into the effects of chamomile specifically on insomnia. One study found that 12 weeks of a herbal extract containing chamomile and *Angelica sinensis* for hot flushes alleviated sleep disturbances as well as fatigue [82]. Another study did not find that chamomile was efficacious in primary insomnia—they found modest but non-significant improvements in sleep latency, night-time awakenings and daytime functioning compared with placebo and no

differences in subjective sleep efficiency and total sleep time [191]. A more recent study investigating the effect of drinking chamomile tea for two weeks in postnatal Taiwanese women found that compared with the control group (regular postnatal care), those drinking chamomile tea had significant improvements in physical-symptoms-related sleep inefficiency and symptoms of depression. The positive effects were immediate rather than long term—when the two groups were compared 4 weeks after cessation of the study, there was no significant difference between the two groups [22].

There is research that indicates the usefulness of chamomile in the treatment of anxiety, and given the links between anxiety and sleep problems, chamomile may be useful as an adjunct treatment in anxious patients with sleep problems. An RCT in people with mild-moderate generalised anxiety disorder found that chamomile extract significantly reduced anxiety in comparison to placebo [4]. Another study found that chamomile oil was associated with increased comfortable feelings and decreased alpha 1 (8–10 Hz) recordings of the EEG in the parietal and temporal regions of the brain [95]. These studies therefore support its use in stress reduction.

Kava

Kava (*Piper methysticum*) is a psychotropic plant from South America that has anxiolytic ability. It is able to modulate GABA activity via alteration of lipid membrane structure and sodium channel function, and can inhibit monoamine oxidase B and inhibit noradrenaline and dopamine reuptake [145]. A systematic review found that the weight of evidence indicates that kava is efficacious in treating anxiety, with significant results in four out of six studies. The review also made several recommendations around safety. These included advising the use of the traditional, water soluble extracts of the root, and avoidance of concurrent alcohol use, avoidance of high doses if driving or operating heavy machinery, and caution with other psychotropic medication. They also advised routine liver function tests for those who used it on a regular basis [145].

In a single-arm study (no control), kava and valerian separately were both found to be effective in reducing severity of stress and stress-induced insomnia [179]. The most common side effects were vivid dreams for valerian (16%) and dizziness for kava (12%) [179]. When this study was extended to assess the efficacy of the combination of valerian and kava, the combination was found to be more efficacious than the single products in reducing insomnia [180]. In this second study, 67% reported no side effects on kava, 53% reported none on valerian and 53% reported none on the combination. The commonest side effects were vivid dreams (for the combination (21%) and valerian alone (16%) and gastric discomfort and dizziness for kava (3%) [180].

Systematic reviews and meta-analyses found that kava was significantly superior to placebo in treating anxiety [126, 127]. Another systematic review concluded that kava has no replicated significant effects on cognition [87].

Passionflower (Passiflora)

Passionflower (Passiflora) is also used to treat problems like anxiety. A systematic review was conducted, however only two studies met the inclusion criteria, a total of 198 participants when pooled. One study indicated that passiflora was as effective as benzodiazepines in alleviating anxiety. The reviewers were unable to draw any conclusions on efficacy or safety due to the small number of studies [104]. Another systematic review of complementary therapies for the treatment of anxiety concluded that there was strong evidence that supplements containing extracts of passionflower were efficacious in treating anxiety symptoms and disorders [83].

*Ashwagandha (*Withania somnifera*)*

The root of the Indian herb Ashwagandha is used in Ayurveda, Indian traditional medicine, and has adaptogenic benefits, helping the body cope with internal stresses such as anxiety and insomnia and external stresses such as toxins [147]. The major biochemical constituents are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides [172].

A review of the literature indicated that Ashwagandha is able to reduce stress and has anti-inflammatory, antitumor, antioxidant, immunomodulatory, haemopoetic, and rejuvenating properties, and exerts a positive effect on the endocrine, cardiopulmonary, and central nervous systems, although the mechanisms of action are not fully understood [102]. It has also been found to have radiosensitising effects as well as antitumor effects in experimental tumors in vivo [34]. Toxicity studies indicate that Ashwagandha appears to be safe [102].

Animal research and clinical trials support the therapeutic use of this herb for anxiety as well as cognitive and neurological disorders, including Parkinson's disease, and inflammation [172]. It is an adaptogen that can be used for patients with insomnia, nervous exhaustion and debility due to stress. It is also an immune stimulant that can be useful in patients with low white blood cells [172].

Animal research has demonstrated anxiolytic and antidepressive effects of Ashwagandha that are comparable to the benzodiazepine lorazepam (for anxiolytic activity) and imipramine (anti-depressant) [172].

A systematic review that included five studies concluded that Ashwagandha was more effective than placebo at alleviating anxiety and stress and that in four out of the five, the results were statistically significant (one study missed out on claiming statistical significance because the p-value was equal to 0.05, right on the cut-off in other words). The reviewers cautioned that there was a high risk of bias in the studies and that because of the heterogeneity of the studies, they were unable to pool the results in a meta-analysis [128].

*Lemon Balm (*Melissa officinalis*)*

Lemon balm has been traditionally used to aid sleep in the case of restlessness or insomnia due to mental stress [59]. Several studies have found that the combination of valerian and lemon balm to be particularly effective. For example, this combination was found to significantly reduce levels of sleep disorders in menopausal women compared with placebo [165]. Another RCT in healthy volunteers found that the combination of valerian/lemon balm was associated with a significantly higher quality of sleep compared with the placebo group, and that is was well tolerated and safe (no serious adverse events were reported, and there was no significant difference in terms of proportion of adverse events in the valerian/lemon balm group compared with the placebo group) [21]. In children under 12 years of age suffering from restlessness and dyskoimesis, in an open, multicentre study, a combination of valerian and lemon balm was found to reduce symptoms markedly (restlessness improved in 70% and dyssomnia improved in 81%), and no adverse events were associated with the medication [109].

Caution is recommended if operating heavy machinery or driving a motor vehicle or doing any activity that requires mental alertness, as this herb may cause drowsiness in some people. In addition, the consumption of alcohol or concurrent use of other health products or medications that have sedative actions is not recommended [59].

Essential Oils

In folklore, people used to put lavender in their pillows to promote sleep when they were restless. There is evidence that aromatherapy with lavender oil may slow the nervous system activity and promote relaxation and sleep. Massage with lavender essential oil may also reduce anxiety, and promote better sleep [168]. In Germany, lavender flowers are approved as a tea for insomnia, nervous stomach irritations and restlessness [168].

Burning lavender essential oil in an oil burner can promote relaxation. The electric oil burners with timers that switch off automatically may be safer than those with candles in case the patient falls asleep.

Homoeopathy

There is some evidence that homoeopathy treatments can assist with insomnia (as well as other symptoms associated with cancer). The following homoeopathic remedies may be useful for particular patients, depending on the nature of their presentation: Coffea Cruda, Nux Vomica, Cocculus, Aconite, Chamomilla, Arnica, Belladonna, Gelsemium, Capsicum, and Staphysagria [113].

A systematic review of four randomised controlled trials that compared homoeopathic medicines to placebos in the treatment of insomnia did not find evidence of a significant difference between treatment and control groups, though two showed a trend favouring homoeopathic medicines. These studies were judged to be of poor methodological quality and probably 'underpowered' (this generally means that they would not have had sufficient numbers of participants to be able to detect a change in the outcome variables they were testing). In addition, one cohort study reported significant improvements compared with baseline, and there were no RCTs that tested out individualisation of homoeopathic treatment [27].

Since that review was published, a higher quality double-blind RCT has been conducted investigating the efficacy of homoeopathic simillimum treatment compared with placebo in the treatment of chronic insomnia. The study found that the homoeopathic treatment resulted in a significant increase in sleep duration compared with placebo. Sleep quality was significantly improved in the homoeopathic group at the end of the study compared to baseline, and compared with placebo [113].

It is important that an experienced homoeopath assesses and prescribes homoeopathic treatments.

Chinese Medicine and Insomnia

Chinese medicine is underpinned by its own philosophies and theories, with its own medical language, and has been practised for over 3000 thousand years. Unlike biomedicine, insomnia is seen as a condition not of the brain or mind, but of the Heart, capitalised to distinguish it from the usual biomedical understanding. The Chinese medical concept of an organ system extends well beyond the anatomical and physiological functioning as we know it in western medicine. For example, each organ system has a particular emotion associated it with, and a sense organ, connected to it via the meridian system. The meridian system is a system of channels throughout the body, within which Qi, a kind of energetic life force, circulates. The Heart, in Chinese medicine, is seen as the 'seat of consciousness' or where the 'mind' is housed [117].

Where the 'Mind' Is Located

In western medicine, of course, we understand the brain to be where 'mind' is located. However scientific research is turning this fixed idea somewhat on its head (pardon the pun, it's intended). One only has to read cardiologist Paul Pearsall's book 'The Heart's Code' [122] and read about memories transferred from heart transplant donors to the recipients to start to wonder whether the ancient Chinese weren't onto something after all. The field of 'neurocardiology' envisages the heart as a sensory organ that can process and encode information and that functions in

concert with the brain but also independently of it [98]. The heart and the gut have their own neural networks. Research has established that in addition to affecting autonomic regulatory centres, cardiac afferent neurological input can also affect higher brain centres involved in emotional processing and perception. Changes in both afferent and efferent autonomic activity have been found to be associated with changes in heart rhythm patterns with positive and negative emotions associated with increased and decreased coherence of heart rhythm respectively [98]. Research has also shown that the heart and brain can receive and process information about future events before the event occurred, and that the heart receives such 'intuitive' information before the brain and sends a different pattern of afferent signals to the brain which modulates the frontal cortex [99].

How Chinese Medicine Views Insomnia

In Chinese medicine, insomnia is seen as a disturbance, fundamentally of the person's 'Shen'. Shen is seen as a rarified form of Qi that resides in the Heart, hence the idea that the Heart is the 'seat of consciousness' [117]. In Chinese medicine, diseases or conditions are subcategorised into underlying syndromes or patterns of disharmony. A syndrome is characterised by particular signs and symptoms that reflect the underlying aetiology and pathogenesis as understood in Chinese medicine. Thus, insomnia has anywhere between 7 and 9 syndromes, according to two published textbooks [45, 97]. Chinese medicine treatment with either Chinese herbal medicine or acupuncture will aim to treat not only the 'disease' or disorder, but its underlying syndrome and as such, the Chinese herbal medicine prescription chosen (Chinese herbal medicine is typically a combination of several herbs chosen judiciously according to Chinese medicine theory) or acupuncture points that make up the acupuncture prescription will differ between syndromes of the disease/disorder (and will generally be tailored to other characteristics of the patient including age, constitution and others) [117].

Acupuncture Treatment of Insomnia

Insomnia is one of several diseases or conditions listed in the World Health Organization [182] Review of Acupuncture as having been shown to have a therapeutic effect but for which further proof was needed [182]. Acupuncture can regulate various neurotransmitters and hormones such as endorphins, serotonin, norepinephrine, adrenocorticotrophic hormone, cortisol, acetylcholine, melatonin, substance P, gamma-aminobutyric acid (GABA), and nitric oxide, known to be involved in sleep regulation [62]. Research has also shown that acupuncture can regulate higher cortical function, the HPA axis and somatovisceral reflexes [62].

Useful acupuncture points

There are several points that are understood to be particularly effective in the treatment of insomnia. These include the acupuncture points: Shenmen (Heart 7), Yintang (Extra point), Neiguan (Pericardium 6) and Anmian (Extra point). Intradermal needles for 3 days at acupoints Shenmen (Ht7) and Neiguan (PC6) was associated with a significant improvement in insomnia-related scales compared to sham acupuncture [88]. Auricular acupuncture points may also be used in the treatment of insomnia.

Clinical research

In clinical research, acupuncture has been found to significantly increase the production of melatonin at midnight and decrease its production during 8 a.m. and 3 p.m. in insomniacs [159]. Acupuncture was associated with a significant decrease in sleep onset latency and arousal index and a significant increase in total sleep time and sleep efficiency. In addition, percentage of time spent in Stage 3 slow wave sleep increased from 4.2% before to 6.1% (normal mean 7%) after acupuncture [159].

Several systematic reviews investigating the efficacy of acupuncture in treating insomnia have been conducted [12, 23, 63, 185, 186]. Although a general criticism of many of the studies was of methodological shortcomings, it appears that there is some evidence that acupuncture may be useful in the treatment of insomnia [117].

Acupuncture is best performed by practitioners trained in traditional acupuncture who are able to diagnose and treat the relevant underlying Chinese medicine syndrome as part of an integrated approach.

Chinese Herbal Medicine

There is evidence to indicate that Chinese herbal medicine treatment of insomnia is efficacious and safe. A systematic review of Chinese herbal medicine in the treatment of insomnia found that 8 of 217 studies met the inclusion criteria. Meta-analysis found that in three studies, efficacy of Chinese herbal medicine was equivalent to that of western medication, and in another three studies, the efficacy was the same as placebo. Due to the small number of studies and their poor methodological quality, the reviewers were unable to find evidence to support the efficacy of Chinese herbal medicine for insomnia. However, they did find that the frequency of adverse events for Chinese herbal medicine was lower than for western medication (and the same as for placebo) [187].

A more recent and much larger systematic review that included 79 randomised controlled trials and 76 in the meta-analysis found that Chinese herbal medicine was more significantly more effective than placebo and benzodiazepine drugs in alleviating insomnia. The effect was also seen for Chinese herbal medicine combined with benzodiazepines compared with placebo plus benzodiazepines or cognitive behavioural therapy alone. There was no significant difference in the frequency of adverse events between Chinese herbal medicine and placebo [115].

Conclusion

Good sleep is vital to health. There is evidence that those who do not sleep well on an extended basis are at greater risk of developing cancer as well as at risk of a range of other diseases and risk factors for disease including obesity, Metabolic Syndrome, diabetes, anxiety and depression. Those who have chronic sleep problems have a greater risk of early death. Clinicians often forget to ask patients about their sleep despite it being one of the pillars of health and something that has such a profound influence on health.

Poor sleep is of itself stressful, and stress can lead to poor sleep. It is therefore important that strategies for improving sleep are integrated into a patient's Wellness Plan. These can include relaxation and other stress reduction techniques, exercise, including in diet those foods that enhance sleep (and avoiding foods that are detrimental to sleep), cognitive behavioural therapy, supplements, western herbs, Chinese herbal medicine and acupuncture and others. There is plenty of evidence to support the efficacy of these strategies. An integrated care approach involving a team of healthcare professionals really is the best way to assist patients with cancer to address sleep disturbances.

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Chapter 5
Vitamin D and Sunshine

Humans are like outdoor plants in relation to sunlight.
Professor Avni Sali.

Introduction

Sunlight is an important factor for health and happiness. Sunlight exposure is essential for the production of Vitamin D, and this vitamin is associated with healthy bones, better moods and other health benefits. Human beings can be considered 'outdoor plants' rather than indoor plants, in relation to sunlight exposure. Think what happens to outdoor plants that are placed inside for too long! Human beings need adequate doses of sunlight. We cannot survive without adequate sunlight exposure.

It seems that human beings do not do very well healthwise when Vitamin D levels are low. There is increasing evidence that shows a link between many health conditions and low levels of Vitamin D. It is Professor Sali's experience that almost without exception, nearly every cancer patient that has consulted him, has had what he considers to be low Vitamin D levels. Sunlight exposure is the best way to get adequate doses of Vitamin D.

This chapter will examine the benefits of sunlight exposure and Vitamin D in relation to cancer. In particular, we will look at the evidence that indicates an association between low Vitamin D levels and cancer. Sunlight exposure can also regulate moods and may be helpful in lifting mood and alleviating depression that can be associated with cancer. Finally, we will discuss some recommendations about sunlight exposure and Vitamin D supplements as part of the Ultimate Consultation.

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What Is Vitamin D?

Vitamin D is the name given to a group of fat-soluble prohormones or precursors of hormones that can be converted into hormones in the body. There are two major forms of Vitamin D: Vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol) [28]. The two forms differ only in their side chain structure and the differences do not affect metabolism (activation) [36].

Vitamin D_2 is largely man-made and added to foods. In contrast, Vitamin D_3 is synthesised from 7-dehydrocholesterol in the skin following exposure to ultraviolet light (UV(B)) and may also be gained through dietary sources [28]. Both Vitamin D_3 and D_2 are synthesised commercially and available as dietary supplements or may be added to foods (fortified foods) [36]. Vitamin D_3 has superior absorbability and efficacy compared with Vitamin D_2 [14].

Metabolism of Vitamin D in the Body

Vitamin D from exposure to the sun, food and supplements is biologically inert and must undergo two hydroxylations, the first one in the liver which converts Vitamin D to 25-hydroxyvitamin D, the circulating hormone precursor, written in shorthand as 25(OH)D, and also known as calcidiol. This then travels to the kidneys to be converted to the physiologically active metabolite, 1α,25-dihydroxyvitamin D_3, written in shorthand as ($1,25(OH)_2D$), and also known as calcitriol. Calcitriol then binds to Vitamin D receptors throughout the body—these complexes then mediate the hormonal actions [22].

Vitamin D_3 from sun exposure is initially synthesised via the initial conversation of 7-dehydrocholesterol in the skin. Other organs can also produce 1,25-dihydroxyvitamin D.

Vitamin D may be stored in adipose tissue; however, this stored Vitamin D may not be readily available for the body's use, with the implication that for people who are overweight or obese, additional doses of Vitamin D supplements may be required in order to achieve a similar level of circulating 25(OH)D as those of normal weight. The products of Vitamin D metabolism are excreted through the bile into the faeces. Very little is excreted via urination [36].

The Role of Vitamin D in the Body

Vitamin D has several important roles in the body, but is best known because of its role in healthy bones. It promotes calcium absorption in the gut and maintains calcium and phosphate levels to enable bone mineralisation, and is required for bone growth and remodelling. Calcitriol-Vitamin D receptor complexes regulate

many different target genes, including those genes that regulate calcium and phosphate metabolism and bone mineralisation. Where there is either an absence of calcitriol, the active hormone, or functional Vitamin D receptors, calcium absorption becomes impaired and bones are not adequately mineralised, leading to rickets in children and osteomalacia in adults [22]. The most common cause of rickets and osteomalacia is Vitamin D deficiency, though there are some rare genetic causes of rickets (see later section). Vitamin D is required, along with calcium in older people to protect against osteoporosis [31].

Vitamin D has numerous other roles in the body, though these are less well known and have only recently been better understood. Vitamin D_3 has a homeostatic function in foetal and adult development, and differentiation in many systems of the body-endocrine, metabolic, neurological, epidermal and immunological [28].

Other Vitamin D Receptors Throughout the Body

Vitamin D receptors are also found widely throughout the body in tissues not involved in calcium and phosphate homeostasis [5]. Vitamin D Receptors (VDRs) are widely distributed throughout nearly every body tissue including bone, pancreatic β cells, parathyroid gland, brain, skin, prostate, testes, heart, skeletal muscle tissue, breast, liver, lung, intestine, kidneys, adipose cells and immune response cells (e.g. macrophages, dendritic cells and activated B cells) [5]. VDRs have also been found in epidermal keratinocytes, activated T-cells, antigen presenting cells, macrophages and monocytes, and cytotoxic T-Cells, but the mechanism by which calcitriol acts in these tissues is not well understood [36]. This widespread involvement of Vitamin D supports its important role in physiological functioning, and indicates a role in homeostasis of many systems, well beyond simply bone mineralisation [5].

Vitamin D Receptors and the Gut Microbiome

Vitamin D receptors are highly expressed in the ileum of the small intestine [40]. There is emerging evidence that the Vitamin D pathway is an important modifier of the effects of intestinal flora on inflammatory disorders [20]. Commensal bacterial colonisation also affects the distribution and expression of Vitamin D receptors in intestinal epithelial cells [51]. Vitamin D plays a role in T-regulatory and dendritic cell development, so it is possible that Vitamin D status could modify the effect of the gut microbiota on the immune system functioning [20]. Research in mice has demonstrated that a lack of Vitamin D receptors is associated with chronic, low grade inflammation of the gastrointestinal tract [52]. Research in animals has demonstrated a critical role for Vitamin D signalling in maintenance of intestinal

integrity, eubiosis and metabolic homeostasis [40]. Vitamin D deficiency was found, in animal research, to decrease the expression of Paneth cell specific α-defensins (which are secreted into the gut lumen to balance the gut microbiome population), which may lead to intestinal dysbiosis and endotoxemia [40]. Thus, research indicates that Vitamin D plays an important role in maintaining a healthy gut microbiome.

Vitamin D Receptor Binding Sites and the Genome

In addition, there are thousands of VDR binding sites throughout the genome controlling hundreds of genes [5]. It has been estimated that calcitriol regulates 1000 different genes governing nearly every tissue [24] or as much as 5% of the human genome [33].

Gene Variants and Vitamin D Deficiency

Recent research has demonstrated a link between genetic variants and Vitamin D deficiency. A large study investigating the genetic determinants of Vitamin D insufficiency analysed data from 15 epidemiologic studies that included over 30,000 white persons of European descent. The study found that there were three common variants near genes involved with cholesterol synthesis, hydroxylation (Vitamin D metabolism) and Vitamin D transportation in blood which influence Vitamin D status. The greater the number of variants an individual had, the greater the risk of low Vitamin D levels: those in the highest quartile for number of gene variants had 2.5 times the risk of having a low blood Vitamin D concentration (defined as <75 nmol/L) than those in the lowest quartile [45].

Vitamin D and Genetic Disorders

There are two types of genetic disorders that cause rickets in children. The first disease is 1α-hydroxylase deficiency also known as Vitamin D dependent rickets type 1 (VDDR-1) or pseudovitamin D deficiency rickets (PDDR). It is caused by a defect in the enzyme 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase) which converts 25(OH)D (the hormone precursor) to calcitriol (the active hormone) [22]. The second disease is hereditary vitamin D resistant rickets, also called Vitamin D dependent rickets type II (VDDR-II). In this disease, the Vitamin D receptors are defective. Both of these are autosomal recessive diseases and are rare. Both are characterised by hypocalcaemia, secondary hyperparathyroidism and early

onset severe rickets, however in VDDR-I, there is extremely low to absent calcitriol levels, whilst in VDDR-II there are excessively high levels of calcitriol [22].

Benefits of Vitamin D

Evidence is accumulating that some of the important functions performed by Vitamin D include the following:

- Strengthening the immune system
- Benefiting the nervous system
- Strengthening the respiratory system
- Cardio-protection
- Assisting with weight management, including carbohydrate and fat metabolism
- Strengthening and promoting healthy bones
- Supporting dental health
- Assisting with overall musculoskeletal function
- Aiding proper digestion and food absorption
- Preventing and treating chronic diseases including cancer, cardiovascular disease, autoimmune illnesses (e.g. Multiple Sclerosis, Irritable Bowel Syndrome)
- Healthy brain function
- Behavioural benefits.

There is increasing evidence that Vitamin D also plays a protective role against neoplasia and recurrent secondary metastasis [28], discussed later in this chapter. It may also play a role in autoimmune diseases such as Multiple Sclerosis (where high circulating levels of Vitamin D have been found to be associated with lower risk of this disease [29]), rheumatoid arthritis [25], type 1 diabetes [15], cardiovascular disease [38] and other diseases.

Measurement of Vitamin D Levels

25OHD is the major circulating form of Vitamin D and is what is routinely measured to provide a patient's Vitamin D status [36, 28]. It circulates bound to a plasma carrier protein called Vitamin D Binding Protein [36]. Thus, it is calcidiol rather than calcitriol that is measured.

It is critical to understand in what season the 25(OH)D level is measured. What may be an 'adequate' level at the end of summer may well be very inadequate at the end of winter when there is inadequate sunlight.

There are some difficulties measuring the 25(OH)D concentrations, however, as there is considerable variability among assays (the two common methods are antibody-based and liquid chromatography) and among laboratories that conduct

the analyses. A standard reference material became available in the US in 2009 that permits standardisation of values across laboratories which may improve the situation [31].

Sources of Vitamin D

Sources of Vitamin D include sunlight exposure, by far the best way to get Vitamin D into the body, and to a lesser extent, via foods and if necessary supplements.

Sunlight

For our bodies to make Vitamin D, we need to be exposed to UV(B) rays. Exposure to sunlight for small amounts of time, even 10 min, can be beneficial for obtaining Vitamin D, however many individuals can need more than 10 min. Generally, no more than 20 min of exposure to 80% of the body to sunlight will allow the skin to produce its maximum daily yield of Vitamin D which equates to 10,000–20,000 IU (250–500 mcg) taken orally [42]. The human body is usually unable to achieve levels of 25(OH)D greater than 100 ng/ml (250 nmol/L), which is considered an undesirable level, on exposure to UV(B) alone [44].

Care should be taken to avoid sunburn, in particular between 10 am and 3 pm when the UV radiation is most intense. Optimal exposure times will vary according to the individual, regional conditions and temperatures.

UV(B) intensity varies with season and latitude, so the further a person is from the equator, the less time in a year they can rely on sun exposure to produce Vitamin D3 [47]. Cloud cover can reduce the UV energy by 50% and shade and severe pollution, especially in large cities in countries such as China, can reduce it by 60% [46]. UV(B) does not penetrate glass and so sun exposure through glass will not produce Vitamin D [13].

Vitamin D made in the skin is not immediately absorbed into the bloodstream—it may take up to 48 h to be fully absorbed. Thus, it is recommended not to wash thoroughly with soap and water the areas of the skin most exposed to the sun for up to two days following significant exposure [42].

Those at Risk of Vitamin D Deficiency

There are a few groups of people who may be more at risk of Vitamin D deficiency. People with dark skin do not produce as much Vitamin D, even when exposed to the sun [42]. It has been estimated that a black person, because of the increased

melanin in the skin, will need up to six times the exposure of a white person to produce the same amount of Vitamin D [6]. Thus, having dark skin means that the person will need a much greater sunlight exposure than having light skin.

Inadequate skin exposure due to various cultural practices will also lead to Vitamin D deficiency. Persons with limited exposure to sunlight will need to incorporate dietary sources of Vitamin D and consider the use of supplements. However, people with Crohn's Disease or coeliac disease may also be more susceptible as these illnesses typically involve fat malabsorption and they therefore will not benefit from Vitamin D in foods and/or supplements [42].

Sunbathing, Sunscreens and the Wisdom of 'Slip, Slop, Slapping'

Sunscreens have been widely promoted to protect against skin cancer, particularly in countries such as Australia which have one of the highest skin cancer rates in the world. In the 1980s there was a widespread media campaign with the catch-phrase 'Slip, Slop, Slap-slip on a shirt, slop on sunscreen and slap on a hat'. It is of interest that over 90% Australians live in big cities and hence a large proportion of the population are actually sunlight depleted.

Sunscreens with a Sun Protection Factor (SPF) of ≥ 8 will block UV(B) rays [50]. People with skin that is sensitive to sunlight exposure, for example, those of Celtic origin, are also more likely to avoid the sun for fear of sunburn, however this can be very detrimental as it can lead to low Vitamin D levels and hence increase the risk of melanoma. Clothing is another method of preventing exposure to UV. Sunscreens and clothing will block Vitamin D production.

The Vitamin D Council recommends that if the intention of sunbathing is to produce Vitamin D, then sunblock creams are not recommended as they reduce the ability of the skin to absorb UV(B). It recommends exposing skin for half the time it takes for it to turn pink, and that overexposure is unnecessary and dangerous as it increases the risk of squamous cell carcinoma and basal cell carcinoma. It believes that the benefits of sensible sun exposure and maintaining adequate Vitamin D levels outweigh the risk of these cancers [44].

Skin Cancer

The risk of skin cancer is inversely proportional to constitutive skin pigmentation, with those with white skin and poor tanning ability being more susceptible to sunburn and skin cancer, than those with darker skin [39]. There has been caution about recommendations of sunlight by the medical profession because of the association between UV exposure and skin cancers. Malignant melanoma, the most

serious of the skin cancers, has been found to be caused by episodes of intermittent, short-term high doses of UV exposure. In contrast, less intense exposure has not been found to be a risk factor for melanoma development; in fact, several studies have found this type of exposure to actually be protective against melanoma [35]. Other types of skin cancer including squamous cell carcinoma and basal cell carcinoma tend to be found on places on the body that are more exposed to the sun and are associated with a lifetime of sun exposure [1].

Diet

There are only a small number of dietary sources of Vitamin D, and generally diet will provide rarely more than 5% of our daily requirements [42]. The best sources of Vitamin D are fatty fish such as salmon, mackerel and fish liver oils (e.g. cod liver oil). Small amounts can be obtained from cheese, egg yolk, fish, meat and beef liver. These primarily provide Vitamin D_3 and its metabolite 25(OH)D_3 [28, 32]. Dietary sources of Vitamin D_2 include UV(B) irradiated yeast and fungi [28]. Mushrooms growing outdoors have the highest Vitamin D levels of all foods.

In the US, fortified foods provide most of the dietary supply of Vitamin D—most of the US milk supply is voluntarily fortified with 100 IU/cup and in Canada milk must be fortified by law. In the US infant formula must contain 40–100 IU of Vitamin D per 100 kcal. In addition, some breakfast cereals, orange juice, yogurt, margarine and other food products may have added Vitamin D [31].

Adequate and Safe Levels

The amount of 25(OH)D that is considered inadequate and adequate for health is controversial. Table 5.1 sets out recommendations of the Food and Nutrition Board of the US National Institutes of Health [31], whilst Table 5.2 sets out the recommendations of the Vitamin D Council [44]. As can be seen by comparing the two, there is quite some difference between what is considered adequate/sufficient and what is the lower limit for potential adverse events.

Recommended Daily Allowances (RDA)

The Recommended Daily Allowance (RDA) is the nutrient intake considered to be sufficient to meet the requirements of 97.5% of healthy individuals [8, 43]. In the case of Vitamin D, the Food and Nutrition Board's (of the Institute of Medicine) RDA is 600 IU per day for individuals 1–70 years of age and is assumed to achieve

Table 5.1 Health status and levels of 25(OH)D: Food and Nutrition Board, National Institute of Medicine (US)

Levels of 25(OH)D	Commentary on health status
<30 nmol/L (<12 ng/mL)	Associated with Vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults)
30 to <50 nmol/L (12 to <20 ng/mL)	Generally considered inadequate for bone and overall health in healthy individuals
≥ 50 nmol/L (≥ 20 ng/mL)	Generally considered adequate for bone and overall health in healthy individuals
≥ 125 nmol/L (≥ 50 ng/mL)	Emerging evidence links potential adverse effects to such high levels, particularly if >150 nmol/L (>60 ng/mL)

Based on data from Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010. And Reprinted from National Institutes of Health (NIH). Vitamin D: Fact Sheet for Health Professionals. Retrieved from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en1. Last Accessed on 8 January 2017

Table 5.2 Levels of 25(OH)D: Vitamin D Council Recommendations

Levels of 25(OH)D	Category
0–100 nmol/L (0–40 ng/ml)	Deficient
100–200 nmol/L (40–80 ng/ml) Target: 125 nmol/L (50 ng/ml)	Sufficient
200–250 nmol/L (80–100 ng/ml)	High normal
>250 nmol/L (>100 ng/ml)	Undesirable
>375 nmol/L (>150 ng/ml)	Toxic

Based on data from Vitamin D Council. For Health Professionals: Position Statement on Supplementation, Blood Levels and Sun Exposure. Retrieved from: https://www.vitamindcouncil.org/for-health-professionals-position-statement-on-supplementation-blood-levels-and-sun-exposure/. Last Accessed on 8 January 2017

serum 25(OH)D levels of 50 nmol/L or more in 97.5% of healthy individuals, this being the level considered beneficial to bone health and to prevent disease and injury [8, 43].

The Food and Nutrition Board of the Institute of Medicine of the National Academies published RDA's for Vitamin D, are set out in Table 5.3.

Whilst these are recommended daily allowances, there has always been controversy about RDAs which are set for large populations rather than individuals. In addition, there has been criticism in the literature about the methodology used by the Institute of Medicine to determine the RDA for Vitamin D with the implication that the RDA is too low to achieve serum 25-hydroxyvitamin D (25(OH)D) levels of 50 nmol/L or more in 97.5% of healthy individuals [43].

Table 5.3 RDA of Vitamin D supplements: Food and Nutrition Board of the Institute of Medicine

Age	RDA
Infants	In the absence of sufficient evidence to develop an RDA, an 'Adequate Intake' level has been set of 400 IU (10 mcg) per day, which should ensure nutritional adequacy
Between 1 and 70 years of age, male and female, including women who are pregnant or lactating	600 IU per day (15 mcg per day)
$\geq$ 71 years or older	800 IU per day (20 mcg per day)

Note These values are based on minimal sun exposure
Based on data from: [30, 31]

Supplements

The Vitamin D Council recommends taking at least 5000 IU of Vitamin D_3 daily for adults (including pregnant and breastfeeding mothers) not exposed to sunlight, which may need to be increased in obese individuals. They also suggest that if pregnant or breastfeeding, it is important to check blood levels to ensure the mother has sufficient Vitamin D levels. They advise an upper limit of 10,000 IU/day, and that if dosing at 10,000 IU/day or higher, blood Vitamin D levels should be monitored every 3 months for the first 12 months and thereafter, every 6 months [44].

Relationship Between Low Vitamin D Levels and Cancer

Vitamin D has been of interest to healthcare practitioners dealing with cancer as much research indicates there is a link between low levels of this vitamin and cancer. Higher circulating serum levels of 25(OH)D have been found to be associated with lower risk of developing cancer and better survival post-diagnosis in several cancers [3, 9, 12, 16, 17, 19, 21, 26, 27, 41, 49, 53]. Inverse relationships between solar UV(B) and mortality rates for about 15 different types of cancer have been demonstrated [12]. Doubling the circulating levels of 25(OH)D from 50 nmol/L (20 ng/ml) which is the threshold for adequacy to 100 nmol/L (40 ng/ml) in women was found to significantly reduce the risk of all invasive cancers combined by 67% [23].

For example, a Norwegian study of 658 patients with breast cancer, colon cancer, lung cancer and lymphoma found that patients with 25(OH)D levels <46 nmol/L at diagnosis experienced shorter survival. The risk of cancer-related death in the group with the highest levels of Vitamin D levels was significantly less (64%) compared with those with the lowest levels. The associations between 25 (OH)D levels and survival were found for all four types of cancer [41]. Another

study found that concentration of 25(OH)D of ≥ 40 ng/ml were associated with a substantial (67%) reduction in risk of all invasive cancers combined [23].

Systematic reviews, considered the gold standard of evidence-based medicine, have found associations between Vitamin D levels and risk of cancer (higher levels are associated with lower risk) [3, 9, 11, 21] and in those with cancer, cancer-related and all-cause mortality [4, 17, 27, 26, 53].

Table 5.4 sets out just some of the studies that have investigated the relationship between Vitamin D levels and breast, ovarian and colon cancer. It will be seen from this table that there is considerable variation between studies, however in general, there is growing body of evidence to support the importance of Vitamin D in preventing cancer and reducing mortality once diagnosed.

Table 5.4 Examples of studies investigating relationship between 25(OH)D and cancer

Breast cancer
• A meta-analysis of five studies found that women who had a higher concentration of 25(OH)D at diagnosis had significantly increased survival rates: those with 25(OH)D levels of 75 noml/L had half the 5–20 mortality rate as those with a lower concentration of 30 nmol/L [27]
• A meta-analysis of nine prospective studies (5206 cases, 6450 controls) investigating the association between circulating 25-hydroxyvitamin D (25[OH]D) levels and breast cancer risk found that there was an association in post-menopausal women but not pre-menopausal women [3]
• A meta-analysis of 30 prospective studies examining the potential relationship between Vitamin D levels and breast cancer incidence and mortality found a weak and non-significant association between Vitamin D intake and blood 25(OH)D levels and breast cancer incidence. However, in breast cancer patients, high blood 25(OH)D levels were significantly associated with lower risk of breast cancer mortality and lower overall mortality [17]
• A study in Korea investigated the association between 25(OH)D status at the time of diagnosis, changes in 25(OH)D status over 4 years post-diagnosis and prognosis of women diagnosed with breast cancer. At baseline, patients were categorised as deficient (<20 ng/ml) or non-deficient (≥ 20 ng/ml) in 25(OH)D, and at follow-up, they were categorised as persistently deficient, improved, deteriorated and persistently non-deficient, depending on whether and in which direction their 25(OH)D levels went. The study found that at a median follow-up period of 85.8 months, those patients with advanced-stage disease or an older age who were not deficient had a significantly better survival compared to those who were deficient. At 1-year follow-up, those who were persistently non-deficient and the improved groups had better survival compared to the persistently deficient and deteriorated groups [19]
Ovarian cancer
• Higher serum 25(OH)D concentrations at diagnosis were significantly associated with longer survival in women with ovarian cancer, though there was no significant association with progression-free survival. There was also no significant association found for 25(OH)D concentrations measured after primary treatment [48]

(continued)

Table 5.4 (continued)

Colorectal cancer
• How much Vitamin D was necessary to prevent colorectal cancer was investigated via a systematic review and meta-analysis which found that a 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level 33 ng/mL in comparison with 12 ng/mL and that a daily intake of 1000–2000 IU/day of Vitamin D3 could reduce the incidence of colorectal with minimal risk [11]
• A systematic review and meta-analysis that included nine studies on Vitamin D intake and nine studies on 25(OH)D levels found that Vitamin D intake and blood 25(OH)D levels were inversely associated with risk of colorectal cancer. There was a 12% reduced risk between the highest and lowest categories of dietary Vitamin D intake. There was a 33% reduced risk in the highest compared to lowest categories of blood 25(OH)D levels. A 10 ng/mL increase in blood 25(OH)D level conferred a reduction of 26% for risk of colorectal cancer [21]
• A meta-analysis of four studies found that those with 25(OH)D concentrations of 80 nmol/L had 60% of the 6–20 year mortality rate of those with a lower concentration of 30 nmol/L [26]
• A meta-analysis of observational studies of serum 25-hydroxyvitamin D level and colorectal, breast and prostate cancer and colonic adenoma found that there was a consistent inverse relationship between serum 25(OH)D levels and colorectal cancer, but no association was found for breast and prostate cancer [9]
• A large observational study in 520,000 Europeans found that levels of 25(OH)D had a significant and strong inverse linear dose-response association with risk of colorectal cancer. The study demonstrated a dose-response decrease in colorectal cancer risk with increasing 25 (OH)D concentration. Those in the highest group had a 40% lower risk of colorectal cancer than those in the lowest group. When a subgroup analyses was performed, it demonstrated a strong association for colon but not rectal cancer [16].
• A case-control study that included people of both genders and multi-ethnicity was conducted to investigate the potential relationship between 25(OH)D levels and risk of colorectal cancer. An inverse trend for colorectal cancer was observed. When colorectal cancer was stratified into colon cancer and rectal cancer, they found that plasma 25(OH)D was associated with a significant reduction in risk of rectal cancer but not of colon cancer [49]
• A study in patients diagnosed with colorectal cancer that investigated whether there was a protective effect of Vitamin D levels against dying from all causes or colorectal cancer found that high pre-diagnostic levels of 25(OH)D were associated with improved survival. Higher levels were associated with a statistically significant decrease in overall mortality (33% reduction in risk, when comparing those in the highest and lowest level groups) as well as colorectal cancer-specific mortality (31% reduction in risk, comparing highest and lowest level groups) [7]
• A study involving 1598 patients with stage I–III colorectal cancer conducted in Ireland and Scotland demonstrated that higher levels of 25(OH)D levels (measured about 15 weeks after diagnosis) was associated with lower risk of all-cause mortality and colorectal-specific mortality (30% and 32% lower risk, respectively, when comparing those in the highest third with the lowest third of concentration levels), over a ten year follow-up period [53]

Physiological Mechanisms of Vitamin D in Cancer

As discussed previously, Vitamin D receptors are widely distributed throughout nearly every body tissue including in immune response cells (e.g. macrophages, dendritic cells and activated B- and T-cells), and this widespread involvement of

Vitamin D supports its important role in physiological functioning and homeostasis of the body [5]. There are Vitamin D Responsive Elements (VDREs) in a large number of genes, some of which are involved in regulation of cell proliferation, differentiation and programmed cell death (apoptosis) [33].

Animal and cell culture research indicates that calcitriol or its analogues can prevent cancer development or retard its progression, once manifest. The mechanisms by which the calcitriol can suppress tumor development are numerous and often cell specific. They include inhibition of cell proliferation (cell cycle arrest, interfering with signalling of growth factors), induction of apoptosis, stimulating DNA damage repair, suppressing angiogenesis, and inducing or suppressing cell adhesion molecules and growth factors that promote cellular homing and metastasis [5, 28].

Vitamin D_3 has been found to inhibit initiators of cellular angiogenesis in several cancer cell lines, promote antioxidant responses and block production of IL-1β in macrophages and therefore inflammation associated with colon cancer progression [28]. It has been found to be able to activate cellular signalling cascades in vitro and promote antioxidant responses, which is relevant given that cancer is associated with hypoxia and oxidative stress. Vitamin D also regulates cell autophagy which is important in preventing tumor progression in vivo [28]. Readers are referred to other sources for a more complete discussion of potential mechanisms of action (e.g. [28]).

It is on the basis of this evidence that Vitamin D deficiency is very likely to be important in the development and recurrence of cancer.

Sunlight, Moods and Depression

Sunlight exposure and vitamin D levels affect mood. Several studies have demonstrated that low levels of Vitamin D are associated with depression [2, 18, 34], though not all have [10]. A systematic review and meta-analysis found that there was a 31% increased risk of depression in people in the lowest category of Vitamin D compared with the highest in cross-sectional studies. Randomised controlled studies are needed to determine whether the association is causal [2]. Another study compared depressive symptoms in participants with low and high serum 25(OH)D levels and investigated whether supplementation with Vit D3 (40,000 IU per week for 6 months) could make any impact. The study found that participants with low 25(OH)D levels at the beginning of the study were significantly more depressed than those with high 25(OH)D levels [18].

A systematic review and meta-analysis of seven randomised controlled trials (3191 participants) concluded that Vitamin D supplementation had a significant effect in participants with clinically significant depressive symptoms or depressive disorder [37]. Another meta-analysis of nine trials of Vitamin D supplementation did not find a significant reduction in depression, however the authors of the study did caution that most of studies focussed on people with low levels of depression

and adequate Vitamin D values at baseline [10]. The results of this study should therefore be interpreted with some caution.

It would appear that Vitamin D deficiency is linked with mood, however further clinical research is required.

Some Local Politics

In Australia, general pathology testing is free under the government's Medicare health system, however in November 2014, the government added a levy on Vitamin D testing. This means that patients must now pay out of pocket for this test, even if it is ordered by their medical practitioner. This is a great concern in a country where over 50% of the population and 70% of the southern states of Australia are Vitamin D deficient [42], and considering the important role of Vitamin D in overall health.

Incorporating Discussion of Sunlight in the Ultimate Consultation

During the Ultimate Consultation, the clinician should ask about sunlight exposure to ascertain whether that the person is deficient in Vitamin D. The patient should be made aware of the association between low Vitamin D levels and disease, plus the best sources of Vitamin D, with sunlight exposure being the principle one. Vitamin D levels need to be measured in order to ensure whether or not the patient has adequate levels.

Strategies to Incorporate into a Wellness Plan

Where low levels of 25(OH)D are found, incorporation of the following strategies into the patient's **Wellness Plan** are indicated:

1. Get out in the sunshine
2. Add dietary sources of Vitamin D
3. Take a Vitamin D supplement where necessary.

1. **Get out in the sunshine**.

Since the best way to get Vitamin D is to expose the skin on a daily basis, advice to the patient would include incorporation of daily sun exposure. If the patient is capable of exercise (see Chap. 6 for the benefits of exercise in patients with cancer), then going for a brisk walk or jog in the open air would seem a good way to get a

dose of Vitamin D and exercise, remembering to advise on prudent exposure according to time of day and UV index levels—these will vary according to where one lives. In general, one will get more UV(B) rays when the sun is high in the sky, and most people will not need more than 20 min' exposure of 80% of their body to allow the body to produce its maximum daily yield of Vitamin D [42]. Even when Vitamin D levels are adequate, getting out in the sunshine will help maintain adequate levels. There is no cause for concern that the sunshine can cause excess Vitamin D in the body either.

2. **Add dietary sources of Vitamin D**.

Part of the Ultimate Consultation involves discussion about habitual diet. Advice on diet can include incorporation of foods high in Vitamin D such as oily fish, eggs, meat, mushrooms or fortified foods such as milk products.

3. **Take a Vitamin D supplement where necessary**.

Vitamin D levels should be monitored in order to ensure that the correct level is obtained, in particular when supplements are prescribed. There is considerable variation in the dosage of supplementation required across individuals. For example, 1000 IU of Vitamin D supplementation may be adequate for one person, but another person may need 5000 IU. One can only ensure adequate dosage by retesting levels after a period of time. The RDA for Vitamin D supplements, recommended by the Food and Nutrition Board of the Institute of Medicine (of the National Academies) in the US, is set out in Table 5.3.

Since Vitamin D can be toxic in excessive amounts, and can lead to calcinosis in soft tissue (e.g. kidneys, heart and lungs) and hypercalcaemia, the clinician should warn the cancer patient not to take more than directed and that in the case of this vitamin, more is not better. Regular blood testing can ensure safe levels. The patient should also be advised that it is not possible to get an overdose of Vitamin D via exposure to sunlight, however excess exposure can lead to sunburn and skin-related problems, so caution is advised.

Conclusion

There is evidence that adequate Vitamin D levels are protective against cancer, and that higher levels of Vitamin D are associated with lower risk of developing various forms of cancer. There is also evidence that those with cancer fare better if they have higher levels of Vitamin D. The best source of Vitamin D is sunlight, though a small amount can be sourced via diet. Supplementation with Vitamin D supplements may be indicated in cancer patients with low Vitamin D. Consideration of

Vitamin D status and addressing it where it is low is an integral part of the Ultimate Consultation.

Key Points

- There is increasing evidence that low levels of Vitamin D increase the risk of many cancers, and in those diagnosed with cancer, the risk of dying of any cause or the cancer itself.
- Sunlight is the best form of Vitamin D. Other forms include dietary sources from foods, and Vitamin D supplements.
- Recommended Daily Allowances are calculated for populations of people. There is considerable variation in the dosage of supplementation required across individuals. One can only ensure adequate dosage by retesting levels after a period of time.
- The amount of 25(OH)D that is considered inadequate and adequate for health is controversial. It is important to take into account the time of year that the concentration is measured in individuals.

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Chapter 6
The Power of Movement: Integrating Exercise

Anywhere is walking distance if you have the time

In this chapter we explore:

- Evidence that physical inactivity is dangerous
- Evidence that physical activity decreases the risk of developing cancer and improves outcomes in relation to cancer
- Detailed evidence in relation to physical activity and colorectal, breast and prostate cancers
- Exercise, obesity and cancer
- Health benefits of exercise in people with cancer
- Exercise during and after cancer treatment
- Weight and physical activity recommendations for cancer prevention
- Integrating exercise into the Ultimate Consultation
- Principles for incorporation of exercise into a Wellness Plan.

Introduction

As Micozzi so simply puts it, the body is meant to move [123]. Evidence supports the theory that humans evolved to be physically active and that sedentary ways of life are unhealthy [190].

There is increasing evidence of the benefits of exercise in preventing cancer, as well as benefits during and after cancer treatment. Exercise is not only safe in most cases for people with cancer but can improve physical functioning including cardiovascular fitness and quality of life [161]. Regular, low-moderate intensity exercise has been shown to improve fatigue, anxiety, mood, self-esteem, cardiovascular fitness, muscle strength, and body composition [53]. However, it is

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important that the exercise prescription is tailored to the individual's needs, cancer type, treatment, specific symptoms, and the presence of other co-morbidities [87]. It is part of improving health in a cancer patient, which not only leads to a better quality of life, but a better prognosis.

The list of exercise-induced changes in cancer survivors reported in 26 studies from a systematic review included:

- Decreases in: nausea, fatigue, symptoms, length of hospital stay, heart rate, blood pressure, psychological and emotional stress, depression, anxiety, and body fat; plus
- Increases in: muscle mass, muscle strength, flexibility, cardio-respiratory fitness, quality of life, and haemoglobin [67].

Exercise is beneficial in helping cancer patients address side effects of treatment, as well as the psychological stresses that often accompany cancer. It can help reduce obesity, a known risk factor for cancer, and a recent study has shown that exercise directly stimulates epinephrine and IL-6-dependent NK cell mobilisation, which suppresses tumor growth [141]. However, stress, as we learned in Chap. 2, can also have a deleterious impact on the body via a number of mechanisms. Unloading of the storage of stress is important, and exercise is one way of accomplishing this.

In This Chapter

The first part of this chapter will explore some of the evidence relating to the dangers of a sedentary lifestyle and physical inactivity, and the benefits of physical activity in cancer prevention as well as post-cancer diagnosis. The role of regular physical activity in reducing abdominal and visceral obesity, well-known risk factors for cancer is explored. The role of exercise in reducing stress, depression, and anxiety that are often present in those with cancer, will also be discussed. When a patient is informed about improved lifestyle and its benefits, it allows them to make positive changes which include integrating exercise into their Wellness Plan.

The second part of this chapter will focus on how to integrate discussion of exercise into the Ultimate Consultation and some guidelines to consider when incorporating physical activity into a Wellness Plan that the patient takes home with them.

Types of Exercise

Exercise may be divided into four main types:

- Aerobic exercise: is any method of improving the cardio-respiratory system
- Anaerobic exercise: is short-lasting, high intensity activity, where the body's demand for oxygen exceeds its supply. Anaerobic exercise relies on energy sources stored in muscles and, unlike aerobic exercise, is not dependent on oxygen. Over time a combination of aerobic and anaerobic exercise can increase the body's metabolism, allowing it to naturally burn calories at a faster rate.
- Progressive resistance or strength training: can be designed to maintain or improve muscular strength, endurance or power. This form of exercise may use body weight, weights, resistance machines or elastic resistance bands to progressively overload the muscle.
- Flexibility training: is designed to maintain or improve the range of joint motion by increasing the length of specific muscles or joint structures [146, 169].

Other ways to categorise physical activity

Physical activity can also be categorised as occupational, household, transport (e.g., travelling to and from work) and recreational. It can also be considered in terms of intensity as: vigorous, moderate, light and sedentary [190]. Other subcategories include 'incidental' forms of exercise (those that are part of daily life, e.g. cleaning, walking to and from work, or around our workplace), and 'intentional' or 'planned' exercise (e.g. jogging, going to the gym, or undertaking group exercise classes). All these terms appear in the literature.

Usual and intentional activities can also be subcategorised by intensity as light (e.g. housework, shopping), moderate (requiring effort equal to a brisk walk, e.g. walking, dancing, leisurely cycling, yoga, doubles tennis), and vigorous (involving larger muscle groups and resulting in faster heart rate and breathing, e.g. jogging, running, skipping, fast cycling, circuit weight training, swimming, etc.) [6].

Evidence that Physical Inactivity Is Dangerous

Sedentary behaviour is any activity done in a sitting or reclining position for a prolonged time [171]. Physical inactivity is not meeting sufficient levels of moderate-vigorous physical activity. These are both understood to be risk factors for cancer [114, 171]. There is clear evidence that sedentary behaviour and physical inactivity are dangerous to our health.

Sedentary Behaviour Decreases Lifespan

A study found that television watching, a sedentary activity, was associated with an increased risk of cardio-metabolic disease, type II diabetes, resulting in a decreased lifespan. Compared with those who watch no television, those who watch an average of 6 h/day as a lifetime average will live 4.8 years less; on average, every hour of television watched after the age of 25 reduces life expectancy by almost 22 min [56, 182].

Physical Inactivity Increases Risk of Death

A large prospective population-based study found that high amounts of daily sitting time increased the risk of myocardial infarction (MI) incidence and all-cause mortality. Sitting for 10 h or more per day was associated with a 38% higher risk of MI and a 31% higher risk of all-cause mortality in comparison with sitting for <6 h/day [139].

Even in older persons who may not be able to adhere to the recommended duration of exercise (recommended by national guidelines), some exercise is beneficial and can lower mortality. A meta-analysis of nine cohort studies (122,000 older adults, mean age 73) found a significantly lower risk of death from all causes (22% lower risk) in those who engaged in low-dose moderate to vigorous physical activity [90].

Physical Inactivity Increases Risk of Developing Cancer

The World Cancer Research Fund/American Institute for Cancer Research 2007 report states that low levels of physical activity are, or may be, the cause of colon, postmenopausal breast, and endometrial cancers, as well as a cause of overweight, or obesity [190]. A recent meta-analysis of 17 prospective studies (total of 857,581 participants) found that sedentary behaviour significantly increased the risk of cancer by 20% [171]. Sedentary behaviour has been found to be associated with a higher risk of particular cancers including endometrial cancer [66, 114, 171], colorectal cancer and its recurrence [35, 114, 120, 171], breast cancer [171] and its recurrence [160]), lung cancer [171], and prostate and ovarian cancer [114]. Low levels of physical activity are associated with increased risk of all-cause and disease-specific mortality in cancer survivors [83].

Physical Activity Improves Health Outcomes in Relation to Cancer

The good news is that there is substantial evidence that low to moderate intensity physical activity protects against cancer in general, which is supported by the World Cancer Research Fund/American Institute for Cancer Research 2nd Expert Report [190] with 'probable' support for prostate and 'possible' support for lung and endometrial cancers [87]. Physical activity that promotes healthy weight is expected to protect against those forms of cancer where risk is increased by being overweight or obese [190], although extreme forms of physical exercise may not be protective. Exercise is not just important for improving cancer outcomes—but for those individuals with other co-morbidities such as cardiac disease, hypertension, diabetes, and those who may be have other immuno-compromised conditions or anxiety and/or depression (pre- and post-diagnosis) [75]. When prescribing exercise, these conditions must be considered when developing an individualised exercise prescription.

The relationship between physical activity and health is continuous, and while there does not appear to be a threshold above or below which no effect is found [190], the health outcomes for specific medical conditions are dependent on the exercise type, quantity, intensity, frequency and duration of exercise training. An accredited exercise physiologist has the knowledge and the skills to tailor the exercise prescription to maximise the health outcomes and minimise any adverse consequences for each individual.

Exercise in general improves a person's overall sense of well-being and health. A healthy person with cancer will do better than an unhealthy one.

Physical Activity Reduces the Risk of Developing Cancer

The literature indicates that engaging in exercise confers benefits in terms of reducing the risk of developing a range of cancers. A recent meta-analysis pooled the results of 12 prospective US and European cohorts (a total of 1.44 million subjects). It was found that in comparison with low levels of leisure-time physical activity, high levels of physical activity were significantly associated with lower risks of 13 cancers, with 10 of these associations remaining statistically significant after taking body mass index (BMI) into consideration [106]. The 13 cancers include: esophageal adenocarcinoma, liver, lung, kidney, endometrial, gastric cardia, myeloid leukaemia, myeloma, colon, rectal, head and neck, bladder, and breast.

Potential mechanisms

Research has elucidated several potential mechanisms by which exercise can positively impact on the processes involved in cancer initiation and progression. For example, exercise may alter tumor initiation events by modifying carcinogen

activation (specifically by enhancing the cytochrome P450 system and enhancing particular enzymes in the carcinogen detoxification pathway such as glutathione-S-transferases), and reduce oxidative damage by increasing several anti-oxidant enzymes and improving DNA and intra-cellular repair [151]. Exercise may also dampen the processes involved in cancer promotion and progression including scavenging reactive oxidative species, altering cell proliferation, apoptosis and differentiation, reducing inflammation, enhancing immune system functioning and suppressing angiogenesis [151].

Aerobic exercise in particular seems to be the best of the various types of exercise (aerobic, resistance and flexibility) for protection against cancer, although there are specific benefits of the other types of exercise. Aerobic exercise has been shown to be protective against cancer via several mechanisms including: changes to inflammatory mediators [141, 151], improvements in immune system functioning, maintaining regular bowel habits and reducing bowel transit time, improving musculoskeletal health [67], positive effects on mood, mental health and depression, and protecting against obesity and metabolic syndrome [87].

Physical Activity Reduces Mortality Risk After Cancer Diagnosis

Engaging in physical activity *after* cancer diagnosis is also important in reducing risk of all-cause death as well as cancer-specific mortality [83, 88, 109, 130]. Research has shown that those people diagnosed with breast cancer [94] and colorectal cancer [120] who increased their physical activity after diagnosis had a reduced risk of death.

Other Potential Health Benefits of Exercise During and/or After Cancer Treatment

There are a range of benefits of exercising during and/or after cancer treatment. These include improvements or preservation of muscle mass, strength, and power, reduction in symptoms and side effects (including nausea, fatigue and pain), increased cardio-respiratory fitness, and increased physical function. Other benefits include increased immune function, increased chemotherapy completion rates, better body image and self-esteem, decreased psychological and emotional distress, depression and anxiety, and a reduction in length of hospitalisation [87].

The next section will look at more evidence relating to the benefits of physical activity in specific types of cancers: colorectal, prostate and breast cancer, with respect to reducing the risk of developing cancer and risk of mortality post-diagnosis.

Colorectal Cancer and Physical Activity

Exercise Reduces the Risk of Developing Colorectal Cancer

There is much epidemiological evidence that higher overall levels of physical activity are associated with lower risk of developing colorectal cancer [4, 12, 24, 74, 120, 170]. A recent meta-analysis demonstrated a 16% reduction in risk of colon cancer associated with high levels of physical activity, compared with low levels [130]. An earlier meta-analysis demonstrated a 22% and 29% reduction in risk of colon cancer in physically active males and females respectively [156].

In terms of intensity, more intense activity is likely to be associated with a greater reduction in colorectal cancer risk in men, though this association wasn't found in women [24]. Other studies have shown, however that non-intensive exercise, e.g. walking, is also extremely beneficial. Walking with a friend, walking near the ocean and walking in nature are likely to be most beneficial, simply because they are enjoyable.

Exercising Reduces the Risk of Mortality Post-diagnosis

Once diagnosed with colon or colorectal cancer, there is clear evidence of the benefits of physical activity in reducing the risk of death due to colorectal cancer and death due to 'any causes' as well as reducing recurrence. A systematic review of six studies investigating the relationship between physical activity and mortality found that physical activity *after* diagnosis was (statistically) significantly associated with reduced risk of colorectal cancer-related death (reductions in risk of 45–61%), indicating a dose–response relationship. Post-diagnosis physical activity was associated with statistically significant reductions (ranging from 23% to 63%) in four of the studies [13].

The research literature suggests that higher levels of exercise are better than lower levels of activity or none. Some of the individual research findings in relation to reductions in mortality are set out in Table 6.1.

Even if a person has been inactive prior to diagnosis, there is evidence that increasing activity post-diagnosis is beneficial. Data from the Nurses' Health Study showed that compared with women who did not change their activity levels, women who did had a 52% reduction in risk of mortality from colorectal cancer and a 49% reduction in risk of death from 'any cause' [120].

Interestingly, there is not convincing evidence that higher pre-diagnosis levels of physical activity are associated with lower mortality in colorectal cancer survivors. A study in 668 males with stage I–III colorectal cancer (analysis of the Health Professionals' Follow-Up Study) [121] and another study in 573 women with colorectal cancer (analysis of the Nurses' Health Study) [120] did not find that the level of physical activity *prior to diagnosis* was associated with all-cause mortality or colorectal mortality.

Table 6.1 Research evidence of reductions in mortality with higher levels of exercise

• A study of women with non-metastatic colorectal cancer (Nurses' Health Study Cohort) found that higher levels of exercise after diagnosis was significantly associated with reduced cancer-specific death and overall mortality [120]
• Increasing amount of physical activity in men with non-metastatic colorectal cancer was (statistically) significantly associated with decreased colorectal cancer-specific mortality and all-cause mortality [121]
• In patients with recurrent colon cancer, increasing physical activity was associated with a borderline statistically significant trend for improved survival after recurrence [98]
• Higher physical activity post-diagnosis in patients with Stage III colon cancer was associated with a significant reduction in overall mortality compared with those who engaged in low levels of physical activity [120]

These studies underline the importance of an optimal exercise prescription for an individual, post-diagnosis.

Impact of Physical Activity on Cancer Recurrence

Physical activity post-diagnosis has been found to reduce recurrence of colon cancer. A study in patients with Stage III colon cancer found that higher levels of physical activity post-diagnosis conferred significant benefits in terms of recurrence-free survival. Patients who engaged in a higher level of physical activity had significant reductions in risk of cancer recurrence compared with those who engaged in little activity [120]. This is most likely related to increased exercise stimulating an increase in IL-6 and the subsequent mobilisation of NK cells, which have been shown to suppress tumor growth [141].

Decreasing Exercise Levels Post-diagnosis May Be Detrimental

Although the results were statistically non-significant, the Nurses' Health Study found that in women who decreased their level of physical activity post-diagnosis, there was an increase in cancer-specific (32% increase) and overall mortality (23% increase) [133].

Breast Cancer

Exercise Reduces the Risk of Developing Breast Cancer

There is clear evidence from prospective studies that higher levels of physical activity are associated with a lower risk of postmenopausal breast cancer with a dose–response relationship, though there is little evidence in relation to frequency, duration or intensity of physical activity [190]. There is more limited research evidence indicating that physical activity may protect against premenopausal breast cancer [190].

Prior History of Exercise Pre-diagnosis Reduces Risk of Breast Cancer Mortality

The literature also indicates that for those who have been diagnosed with breast cancer, a prior history of exercise offers some reduction in the risk of death from breast cancer [91, 94, 106]. A systematic review found that pre-diagnosis physical activity significantly reduced all-cause mortality (by 18%), and breast cancer mortality in women with BMI <25 kg/m^2 but not those with higher BMI [91]. Another meta-analysis found that those who reported high lifetime recreational physical activity pre-diagnosis had a significantly lower risk of all-cause mortality (18% reduction) and breast cancer-related mortality (27% reduction) compared to those who reported low or no recreational physical activity pre-diagnosis [106].

More recent pre-diagnosis physical activity was also associated with a significant reduction in risk of all-cause death and breast cancer-related death [106].

A study in women with breast cancer found that women who were active (approximately 2–3 h brisk walking per week) in the year *prior to diagnosis* had a 31% lower risk of death compared with inactive women [94].

Exercise and Breast Cancer Recurrence and Mortality

Systematic reviews and meta-analyses indicate that physical activity confers benefits in those diagnosed with breast cancer in terms of decreased all-cause mortality, breast cancer mortality and breast cancer recurrence [15, 91, 106]. There is an inverse relationship between physical activity and all-cause and breast cancer-related death, and breast cancer events (breast cancer progression, new primaries and recurrence) [106]. There is also evidence that post-diagnosis physical activity reduces all-cause mortality regardless of BMI [91]. Thus, physical activity in and of itself confers benefits.

In women who have previously been inactive, increased activity after diagnosis confers protection, however, decreasing activity can increase risk greatly. A study found that compared with women who were inactive before and after diagnosis, those who increased their physical activity had a 45% lower risk of death, and those who *decreased* their physical activity had a fourfold greater risk of death [94]. Thus, even if a woman has been previously inactive, engaging in increased physical activity is beneficial and should be strongly encouraged. See Table 6.2 for some facts and figures.

To Walk or to Run?

A recent study comparing the benefits of walking versus running post-diagnosis in breast cancer survivors found that running is associated with significantly greater reductions in breast cancer mortality than walking [192]. However, it should be noted that those who are already much fitter and healthier would be more likely to choose to run than those who aren't. Any recommendation of whether to walk or run would depend on pre-existing lower limb musculoskeletal conditions, such as arthritic pain, or biomechanical abnormalities, and the individual's weight. The interesting finding was that the amount of exercise that afforded protection was

Table 6.2 Selected studies of exercise in breast cancer survivors

• A meta-analysis of 22 prospective cohort studies found that those who had the highest level of physical activity *post-diagnosis* had a significantly lower risk of all-cause death (42% reduction) and breast cancer-related death (41% reduction), in comparison with the lowest level of activity. Pre- and post-diagnosis activity was associated with decreased risk of breast cancer events (28% reduction for progression, 21% reduction for new primaries and recurrence combined) [106]
• The After Breast Cancer Pooling Project that combined findings of four studies on women with breast cancer (approximately 18,000 women) found that meeting the recommended 2008 Physical Activity Guidelines was associated with a 27% reduction in all-cause mortality, and a 25% reduction in breast cancer mortality compared to women who did not meet the Guidelines, but that risk of breast cancer recurrence was not associated with meeting the PA Guidelines [15]
• A systematic review of six studies (12,108 patients) of post-diagnosis physical activity was associated with a 34% reduction in breast cancer mortality; in those with oestrogen-receptor (ER) positive breast cancer, post-diagnosis physical activity was associated with a 50% reduction in breast cancer-related death and a 64% reduction in all-cause mortality (HR 0.36), however there was no significant change in relation to ER-negative breast cancer [91]
• A study in women with breast cancer found that women who were more active (approximately 2–3 h brisk walking per week) two years *following diagnosis* had a 67% lower risk of death than inactive women [94]
• A study of almost 3000 women with breast cancer found that greater physical activity was associated with lower rates of all-cause and breast cancer-specific mortality [88]

greater than current general public health recommendations for physical activity; i.e. 150 min/week or 30 min, 5 times/week [192]. This suggests that in breast cancer survivors, at least, the goal shouldn't merely be to satisfy the general public health recommendations, but to exceed these.

Prostate Cancer

Exercising Reduces the Risk of Developing Prostate Cancer

A review of 13 cohort studies conducted between 1989 and 2001 found that the majority reported an association between increasing levels of exercise and decreased prostate cancer risk. Sixteen out of 27 studies performed between 1976 and 2002 found reduced risk in men who were most active, with the average risk reduction being 10–30% [179].

Exercise Is Associated with Lower All-Cause and Prostate Cancer-Related Mortality

The literature supports the contention that higher levels of physical activity are associated with reduced risk of dying from prostate cancer or other causes [22, 103].

- A large cohort study in Sweden indicated that in men with localised prostate cancer, higher levels of physical activity after cancer diagnosis was associated with significantly reduced rates of overall (31–41% lower) and prostate cancer-specific (29–44% lower) mortality [22].
- Analysis of data from the Health Professionals' Follow-Up Study found that engaging in greater physical activity was associated with a 33% reduction in all-cause mortality and 35% reduction in prostate-related cancer mortality compared with those engaging in less activity per week [103].

Benefits have been found for both non-vigorous and vigorous activity:

- Men doing 5 to <10 h/week and $\geq$ 10 h/week of non-vigorous activity had a 28 and 51% reduction in total mortality, respectively, compared to less than 1 h/week [103].
- Vigorous activity was inversely associated with total mortality; all-cause mortality was reduced by 49% and prostate cancer mortality was reduced by 61% in men engaging in $\geq$ 3 h/week of vigorous activity compared with men engaging in <1 h/week [103].
- Men who engaged in $\geq$ 3 h/week of vigorous activity had a 37% decreased risk of prostate cancer progression compared to men who engaged in no vigorous activity [148].

Table 6.3 Research findings in relation to walking

The Health Professionals' Follow-Up Study found that in men with prostate cancer: • Walking for ≥ 7 h/week was associated with a 36% reduction in risk of all-cause mortality compared with <20 min per week • Men with a normal pace has a 37% lower risk and men with a brisk or very brisk pace had a 48% lower risk of all-cause mortality compared with men with an easy walking pace • Those who walked 90 or more minutes per week at a normal (2.0–2.9 mph) to brisk walking pace (≥ 3 mph) had a 46% lower risk of all-cause mortality compared with walking at an easier pace (<2.0 mph) for a shorter duration [103]
A prospective study of 1455 men with localised prostate cancer found that: • Walking pace was associated with decreased risk of progression of the disease independent of duration with a 48% reduction associated with brisk walking relative to walking at an easy pace • Men who walked briskly for ≥ 3 h/week had a 57% lower rate of prostate cancer progression compared to men who walked at an easy pace for <3 h/week [148]

Walking—The Argument to up the Pace

Walking has been found to be beneficial in reducing risk of all-cause mortality and prostate cancer-specific mortality in men with prostate cancer [103]. It seems that brisk walking confers more protection than slow walking in terms of lower risk of all-cause mortality [103] and risk of disease progression [148]. Table 6.3 sets out some of the research findings.

However, what is often missed in designing studies into physical activity is that there are many other associated factors that may impact beneficially on health—for example, walking with a friend (social and peer support) or dog (pet therapy) or merely allocating some 'me time' that contributes to happiness and therefore is likely to improve body function. Such activity usually improves exercise compliance. Thus, caution needs to be taken in interpreting exercise studies conducted under clinical conditions which don't take these other beneficial factors into account.

Other Benefits of Exercise in Prostate Cancer Survivors

There is clear evidence from systematic reviews that exercise confers benefits on men diagnosed with prostate cancer, including improved quality of life, improved lower body strength, exercise capacity, and fitness level and decreased cancer-specific fatigue [23, 128]. Vigorous exercise in men has been found to be associated with larger and more regular vessel morphology in prostate tumors (in contrast, in animal models it has been found that small and irregularly shaped vessels in prostate tumors were associated with fatal prostate cancer) [181].

Research has demonstrated that exercise during and after treatment has been found to positively impact on quality of life in prostate cancer survivors, improve

cardiovascular fitness and self-esteem and reduce the risk of incontinence [20, 39, 129, 188]. Moderate physical activity both during and after treatment of cancer can help to maintain or increase muscle mass and reduce fat mass and to improve cardiovascular fitness, self-esteem and quality of life (QOL) [39, 187]. Resistance and strength training is especially important to maintain muscle and bone mass for men with prostate cancer who have been prescribed androgen deprivation therapy [69]. Research has demonstrated that men undergoing androgen deprivation therapy can safely participate in resistance training without an adverse effect on their testosterone levels [69].

Physical Activity and Other Cancers

There is consistent evidence that higher levels of physical activity (both occupational and recreational) is associated with lower risk of endometrial cancer [190]. For example, six studies demonstrated significantly reduced risk of endometrial cancer, with the risk being reduced by 23–59% in those engaging in the highest level of physical activity compared with the lowest level [190]. There is limited research evidence that physical activity protects against lung cancer and pancreatic cancer. Two studies reported a significantly lower risk (52% and 55%) of pancreatic cancer in those engaged in the highest level of activity compared with the lowest [122, 190].

Exercise, Obesity and Cancer

A significant proportion of high-income populations include people who are overweight or obese. In the US, 2007–2008 figures indicated that 68% of adults $\geq$20 years of age and 17% of children aged 2–19 years are overweight or obese [134]. In Australia the figures are not too dissimilar. Research in 2014–2015 indicates that the percentage of overweight or obese adults ranged from 53% in Northern Sydney to 73% in country regions of South Australia [10]. This is obviously very concerning as being overweight or obese is a risk factor for all-cause mortality as well as a range of specific diseases, including cancer.

Weight, weight gain and obesity have been estimated to account for approximately 14% of all cancer cases in men and 20% in women [29]. Around 4% of new cases of cancer in men and 7% in women in the US are due to obesity, however the figures vary considerably and are much higher for certain cancers such as endometrial and esophageal adenocarcinoma [135]. Obesity is associated with an increased risk of a range of cancers including: esophageal, pancreatic, colorectal, breast (postmenopausal), endometrial, renal, thyroid, gallbladder [134, 190] and aggressive prostate cancer [65]. Table 6.4 sets out some of the figures. What is also very concerning is that there are a significant percentage of cancer survivors who

Table 6.4 Association between obesity and cancer

• Obesity is the cause of an estimated 11% of colon cancer cases, 9% of postmenopausal breast cancer cases, 25% of kidney cancer cases, 39% of endometrial cancer cases and 37% of esophageal cancer cases [92]
• Obese and overweight women have 2–4 times the risk of developing endometrial cancer (not related to menopausal status) [134]
• Obese people are also almost twice as likely to develop esophageal adenocarcinoma [134]
• Body Mass Index (BMI) was found to be significantly associated with higher mortality rates associated with the following cancers: esophageal, colorectal, liver, gallbladder, pancreatic, renal, non-Hodgkin's lymphoma and myeloma, with significant trends of increased risk of death from cancers with higher BMI for stomach and prostate (men) and breast, uterus, cervix and ovary (women) [29]
• The World Cancer Research Fund and American Institute for Cancer Research 2nd Expert Report found that epidemiological data supported a dose–response in relation to BMI and esophageal adenocarcinoma, colorectal, kidney, endometrial, postmenopausal breast, pancreatic cancer and that there is convincing evidence that greater body fatness is a cause of these forms of cancer [190]
• Greater body fatness is a probable cause of gallbladder cancer but there is only limited evidence that body fatness is a cause of liver cancer [190]
• Body fatness has been found to be protective for premenopausal breast cancer [190]

are overweight or obese, and who do not adhere to public health physical activity recommendations. For example, over 65% of breast cancer survivors are either overweight or obese, with less than 30% engaging in the recommended physical activity levels [95].

Abdominal Adiposity

There is a relationship between abdominal adiposity and risk of particular cancers. The World Cancer Research Fund/American Institute for Cancer Research 2nd Expert Report found convincing evidence that body fatness is a cause of colorectal cancer with a dose–response relationship, and probable evidence for an association between abdominal fat and increased risk of pancreatic, endometrial and postmenopausal breast cancer [190]. BMI is highly associated with increased risk of colorectal cancer in men, with abdominal adiposity showing the strongest association [134].

Weight Gain in Adulthood

Weight gain in adulthood has been linked with a range of cancers. The World Cancer Research Fund/American Institute for Cancer Research 2nd Expert Report advised that there substantial and consistent epidemiological evidence of an

increased risk of postmenopausal breast cancer with increasing amount of weight gained in adulthood, with an apparent dose–response relationship. It concluded that adult weight gain is a probable cause of this cancer [190].

Cause-Effect Relationship Between Obesity and Cancer

There is sufficient evidence of a cause-effect relationship between obesity and cancer, however the mechanisms by which obesity may increase the risk of cancer may differ depending on the type of cancer [149, 187]. For example, obesity may be associated with low-grade inflammation which is involved in the pathogenesis of cancer (as well as Type II diabetes and other cardio-metabolic conditions and many other chronic conditions) [134]. Insulin pathways (specifically hyperinsulinemia) appear to mediate the relationship between obesity and colon cancer [79, 187]. For evidence in relation to mechanisms, readers are referred to other reviews.

Weight Loss and Its Impact on Reducing Cancer Risk, Recurrence and Mortality

Despite many studies that indicate an association between overweight and obesity with cancer, there is much less research on the effects of weight loss on risk of cancer [187].

Several studies have demonstrated that weight loss following bariatric surgery reduces risk of cancer [1, 33, 119, 173]. For example, one study found that weight loss after bariatric surgery significantly reduced cancer death by 60% [1]. A systematic review that included 13 studies and 54,257 participants confirmed that bariatric surgery was associated with reduced cancer risk in morbidly obese persons [31].

Other studies have implicated weight loss in reduction of cancer recurrence. For example, the Women's Nutrition Intervention Study that investigated a low-fat dietary intervention in breast cancer survivors found that the average weight of those in the intervention group (target 15% of energy from fats) significantly decreased whilst those in the control group increased. Those in the intervention group had significantly less breast cancer recurrence at 60 months. It is possible that not only the low-fat diet but the weight loss contributed to the results [18].

Overweight and obesity can lead to insulin resistance and Metabolic Syndrome and diabetes. Chronically elevated insulin levels can lead to tumor growth [28] and insulin resistance has been linked to breast cancer [101, 174]. These conditions are risk factors for cancer. Weight loss has been found to be associated with a reduced risk of incidence of diabetes [84].

Physical Activity and Weight Loss

Physical activity can play a role in reducing weight in those who are overweight or obese, however physical activity in itself has a protective effect against cancer, quite independent of its effect on weight [190]. Of interest is the finding from the Nurses' Health Study that examined associations between BMI and physical activity in 116,564 women aged 30–55 years. They found that increased adiposity and reduced physical activity are both strong and independent predictors of death from any cause, and that *weight gain* in adulthood was also a strong and independent risk factor for early death, regardless of exercise level. When the data for cancer-related deaths was examined, the trend was similar- increasing adiposity was associated with an increased risk of death in all three categories of physical activity. Women who were lean and exercised more had the lowest mortality [89]. These results suggest that physical activity may not fully counteract the negative impact of adiposity on risk of all-cause mortality, and nor does leanness counteract increased mortality due to inactivity. Thus, reducing weight for those cancer patients who are overweight *and* increasing physical activity would both seem important. Simply losing weight without increasing physical activity may not be enough either. Those with cancer who are at a healthy weight still need to exercise, given the independent protective effect of physical activity.

Combining exercise and diet

In addition, research suggests that exercise combined with diet is more effective than physical activity alone in reducing weight. A systematic review that investigated the effect of exercise on body weight in men with prostate cancer found that exercise alone did not lead to weight loss (though most of the trials in the review were focused on the impact of exercise on quality of life and fitness rather than decreasing weight); it was diet or diet plus exercise that was found to lead to decreased body weight [128]. It is also important to add in respect to any change in body weight with diet and/or aerobic exercise for men with prostate cancer being treated with androgen deprivation therapy, that any loss of body weight may not be due to a reduction in body fat levels but rather a loss of muscle and bone mass. Hence the importance of including resistance training to maintain or increase muscle and bone mass in this group of clients [69].

What should be the focus of physical activity: weight loss or cardio-respiratory fitness?

The issue of weight loss and physical activity needs to be considered carefully, particularly in overweight or obese people. Weight loss has traditionally been the target in overweight or obese people, and health authorities have recommended physical activity for obesity reduction based on the belief that the ensuing weight loss is the important factor [154]. However, is it the weight loss or the increased cardio-respiratory fitness that should be emphasised as the goal of physical activity, in particular as a treatment strategy in cardio-metabolic disease and longevity [76]? Research suggests it is increased levels of physical activity that is the more important.

The literature supports the contention that increasing cardio-respiratory fitness is more important than reducing body weight in improving cardio-metabolic health and all-cause mortality [76, 105, 110]. Increased levels of cardio-respiratory fitness are associated with lower risks of cancer (as well as all-cause mortality) [97]. There is much evidence to indicate that increased levels of physical activity is associated with significant decreases in cardio-metabolic diseases as well as all-cause mortality [140], but also that a reduction in BMI is not associated with decreased incidence of all-cause mortality [19, 85, 110], unless the individuals were unhealthy [85]. A meta-analysis of 26 studies found that where individuals are healthy and obese, intentional weight loss has no effect on all-cause mortality but where individuals are *unhealthy* and obese, intentional weight loss reduced all-cause mortality by 27% [85].

There is sufficient research that indicates that benefits associated with increased physical activity are not simply related to weight loss [154]. A review of 28 exercise training studies of 8–24 weeks duration found that there were significant gains in cardio-respiratory fitness and significant decreases in waist circumference (marker of abdominal obesity), visceral fat levels and cardio-metabolic risk factors, despite minimal or no change in body weight of those participating [154]. Studies have shown that waist circumference and visceral fat significantly decrease with exercise, with little or no weight loss [152, 153], however there are other studies that have shown the waist circumference and visceral fat decreases with weight loss [154]. Increased physical activity and related improved cardio-respiratory fitness has been found to be associated with significant reductions in coronary artery disease and CVD mortality, independent of weight or BMI [108, 185], and significant reductions in several cardio-metabolic risk factors, with no or little change in body weight [47, 177]. Research indicates that weight loss is not required in order to achieve significant increases in aerobic capacity, and results in significant reductions in blood pressure and resting and submaximal heart rate and positive improvements in mood in overweight/obese men and women [105].

Australian-accredited exercise physiologist Dr Ian Gillam highlighted that changes in body weight itself is a poor indicator of changes in body composition, and that it is the visceral body fat levels that are key determinants of metabolic health and not decreases in body weight [76].

Other Health Benefits of Exercise in People Living with Cancer

In this section, we will look at some of the research evidence in relation to the beneficial impact of exercise on some of the symptoms and co-morbidities associated with cancer in more detail. Systematic reviews of interventions promoting exercise have reported a range of benefits in people living with and beyond cancer including improved health-related quality of life, functional capacity and physical fitness and reduced fatigue and depression [46, 63, 87, 124, 125, 138].

Many people with cancer have co-morbidities including hypertension, cardiovascular disease and others. Therefore, in thinking about how physical activity might positively assist cancer patients, it must also be emphasised that the health benefits of physical activity and fitness are important to the total health and well-being of the individual.

Exercise and Cancer-Related Fatigue (CRF)

Cancer-related fatigue (CRF) is defined as 'a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning' [126]. It affects an estimated 70–100% of cancer patients, seriously interfering with their quality of life [2]. Almost all patients who undergo treatment experience CRF, with almost half reporting it as severe, and it can last for months or years after treatment [132]. CRF is associated with several co-morbidities including sleep problems, depression and pain [132].

There is substantial evidence from systematic reviews [45, 51, 104] and individual studies that regular exercise can reduce fatigue in patients with cancer [40, 41, 168]. In one study of men with prostate cancer with or without androgen deprivation therapy (ADT), 24 weeks of resistance training and aerobic exercise both mitigated fatigue and in the longer term, increased muscle and bone mass, improved body composition and had additional benefits for quality of life [70, 168]. In another study, colorectal cancer patients undergoing chemotherapy who engaged in moderate intensity walking and a flexibility program for 20–30 min/day, 3–5 days/week had significant improvements in cancer-related fatigue (CRF), depression, anxiety, cardiopulmonary function and emotional, functional and physical well-being and quality of life [40, 41].

Muscular Fitness and Physical Functioning

Studies in men with prostate cancer have indicated that exercise is associated with increased quality of life, muscular fitness and physical functioning, and reductions in BMI and body weight [63, 70, 73, 104, 178]. A systematic review in men with prostate cancer found that exercise was associated with improvements in muscular endurance, aerobic endurance and overall quality of life and reduced fatigue [104]. It may also improve muscle mass, muscular strength, functional performance and health-related social and physical quality of life [104]. Strength training is especially important for patients with prostate cancer undergoing ADT [79]. The effects were found to be greater for those engaged in group-based exercise than home-based exercise [104], which is in contrast with another meta-analysis that found comparable benefits [62]. Both low-intensity and high-intensity exercise

training interventions have been found to improve cardio-respiratory fitness in breast cancer and prostate survivors, though four months later, only the high intensity group maintained their cardio-respiratory fitness [115].

Exercise and Glycaemic Control in Diabetics

Interval walking training where the intensity of the training alternates (i.e. three min of low intensity then three minutes of high intensity walking), has been found to better control blood glucose in people with type 2 diabetes, in comparison with continuous walking [102]. A study in type 2 diabetics found that whilst no exercise was associated with a deterioration of glycaemic control, continuous walking had no impact on glycaemic control but interval walking improved physical fitness, body composition (fat mass and visceral adiposity) and glycaemic control [102]. Thus, in cancer patients who may also have diabetes, there may be benefits in trying interval walking training (providing that there are no contraindications that would prohibit this, of course).

Exercise and Hypertension

Exercise is known to have benefits on the cardiovascular system, including lowering blood pressure. For those patients who have hypertension, research has shown that four sessions of 10-min of walking is just as effective in lowering blood pressure as 40 min of continuous walking per day [58]. Therefore, it is not necessary to have a large stretch of time for exercise—breaking exercise periods up into shorter sessions can still have benefits.

Exercise and Cachexia

Cancer cachexia is a complex syndrome characterised by inflammation, body weight loss and continuous loss of skeletal muscle mass (with or without loss of fat) and is a cause of death in a substantial proportion of those with cancer [7, 82]. Cachexia is associated with reduction in muscle strength and endurance, and can be extremely debilitating, reducing quality of life and the ability to perform daily activities. The underpinning mechanisms include lipolysis, changes in muscle metabolism and systemic inflammation [81].

The rationale for the use of exercise to address cancer cachexia is that it is a condition underpinned by systemic inflammation, where muscle strength and endurance are decreased. Exercise can increase muscle strength and endurance in healthy conditions (depending on the type of physical activity) [7], and exercise is

able to exert an anti-inflammatory effect and can counteract the muscle catabolism by increasing protein synthesis and reducing protein degradation [5, 81]. Muscle wasting is only one of the features of cachexia, so exercise is an important strategy to address the underlying systemic inflammation associated with cachexia, not just the muscle wasting. Resistance training and aerobic training may both be able to address this underlying systemic inflammation [71, 113], with several studies of aerobic exercise demonstrating decreased inflammation [11, 157].

Systematic reviews also provide some limited data that exercise can assist in cancer cachexia. A meta-analysis demonstrated that globally, there is a positive effect of exercise in addressing cachexia [142]. Other evidence comes from individual studies, with more focussed on strength training rather than aerobic training (possibly due to the focus on muscle wasting associated with cachexia). See Table 6.5 for some examples.

Anaemia and Exercise

Anaemia is often associated with cancer cachexia (up to one third will have anaemia at diagnosis) and contributes to weight loss, reduced exercise capacity and changes in energy homeostasis [26]. Animal studies have found that when mice with tumors that had a significant decrease in haematocrit were exercised, their condition worsened [7]. The American Cancer Society Expert Panel advise that cancer survivors with severe anaemia delay exercise until anaemia is improved [6].

Table 6.5 Studies supporting benefits of exercise training in cachexia

• A physical activity training program involving low and high intensity resistance training plus massage, relaxation and body awareness training over 6 weeks (9 h/week) in cancer patients undergoing chemotherapy was associated with a significant increase in muscle strength (41%), aerobic fitness (14.5%) and 1% increase in body weight (compared with baseline) [145]
• Resistance training in men with prostate cancer receiving ADT therapy over 20 weeks prevented loss of muscle mass: whole lean body mass and fat mass did not change, muscle thickness significantly increased by 15.7% (quadriceps), muscle strength and endurance significantly increased [68]
• 20 weeks of resistance training in prostate cancer patients receiving ADT therapy was associated with a significant increase in serum growth hormone (GH), dehydroepiandrosterone (DHEA), interleukin-6, TNF-α and differential blood leukocyte counts following acute exercise and did not appear to compromise testosterone suppression [70]
• Resistance training for 24 weeks in men with prostate cancer receiving radiation therapy with or without ADT was associated with longer term improvements in body fat, strength, quality of life and triglycerides [168]

Exercise and Anxiety, Depression, Mental Outlook and Quality of Life

Evidence from case studies, cross-sectional studies, experimental studies and systematic reviews/meta-analyses indicate that exercise can reduce the symptoms of depression and anxiety [25, 36, 43, 46, 51, 100, 118, 166, 193], though a few have found otherwise [45, 180]. Whilst many studies have focussed on aerobic exercise (i.e. walking and jogging programs), others have demonstrated the benefits of non-aerobic, resistance-training programs. Studies that have compared the two types of exercise, aerobic and resistance training, have found they are similarly effective in reducing depression symptoms [21, 55, 71, 116]. Furthermore, the benefits of exercise in reducing depression were found to be maintained months after cessation of the studies [48, 54]. Table 6.6 sets out a few of the studies on exercise, depression and anxiety.

Body image can often take quite a battering in women who have had mastectomies. There are many studies in women with breast cancer including a meta-analysis (of 56 studies) [51] which have demonstrated the positive effects of physical activity on quality of life and positive body image [40, 41, 63, 144, 175]. For example, women with breast cancer who undertook a 12-week exercise regime had significantly improved body image compared with controls, and a non-significant reduction in distress [144].

Exercise as Social Therapy

Exercise may provide an important opportunity for peer support, socialising and unloading of stress. Men with prostate cancer undergoing a structured exercise

Table 6.6 Selected studies of exercise and depression and anxiety

• A meta-analysis of 25 RCTs of exercise interventions in people with depression found that exercise had a large and significant effect on depression [166]
• Analyses of 37 meta-analyses (focused on the impact of exercise on anxiety and depression) suggests that the beneficial effect of exercise is more pronounced in depression compared with anxiety [184]
• An 8 week study without a control group found that patients with generalised anxiety disorder who completed daily exercise improved and the gains were still there 12 months later [117]
• A systematic review of exercise in men with prostate cancer found that exercise was associated with a significant improvement in quality of life and reduction in fatigue but not depression or anxiety [180]
• An Australian study in men with prostate cancer found that inactive men had greater anxiety and higher global distress that those who were insufficiently active (statistically significant) or sufficiently active (not significant statistically) [72]

program reported positive changes in self-efficacy, reduced treatment-related side effects, a shift towards a positive outlook and desire to engage more actively in life as a result of the program. The study found that exercise physiologists provided important information as well as emotional and social support and that peer support of others with prostate cancer that occurred as part of the exercise program was important to these men, in particular sharing the experience of prostate cancer and the social connections that developed as part of the program [37].

Exercise and Sleep Problems

As discussed in a previous chapter, nearly 45% of cancer patients experience problems sleeping, almost three times the proportion in the general population. Disturbed sleep in cancer can be related to pain (due to the disease itself or treatment side effects), psychological stress, and/or the treatments (chemotherapy, radiation, hormone therapy, surgery) and their side effects. Exercise can help combat disrupted sleep. See Chap. 4 for a discussion on sleep.

Exercise and Pain Relief

Pain is experienced in 45–59% of cancer patients and survivors [32], and can be the result of the tumor itself or the cancer treatment including surgery, chemotherapy, radiation therapy, targeted therapy, diagnostic procedures and supportive care [135]. Pain severity and duration correlate with risk of depression [135].

The general pain literature indicates benefits of exercise in relieving chronic pain, largely through the induction of endorphins but also via its positive effect on mood, relaxation of muscles and its anti-inflammatory effect [143]. There is evidence that in cancer survivors, exercise is also beneficial in reducing pain. For example, approximately 20–50% breast cancer survivors experience breast or chest wall pain, impacting negatively on quality of life and research has found that exercise is able to reduce these symptoms and improve quality of life [189]. Aromatase inhibitors used to treat postmenopausal women with hormone-receptor positive breast cancer to help prevent recurrence can cause joint pain and stiffness; exercise (two supervised weight-training and resistance-training sessions, and 150 min of moderate aerobic exercise a week) was found to significantly reduce joint pain and stiffness (20% reduction) compared to women who didn't exercise (3% reduction) [93].

Exercise and Cognitive Impairment

Many cancer survivors, including those with central nervous system (CNS) tumors and non-CNS tumors, suffer the difficulty of cognitive impairment which can include short-term memory, attention, concentration and executive functioning problems and difficulties with word-finding and multi-tasking [9, 96, 132, 159, 183]. It can occur prior to, during and after treatment [96, 183] and it can interfere with their functional independence [159]. Cancer treatments that causes cognitive decline include chemotherapy, radiation therapy, immune modulation, hormone therapy, pain medications and brain surgery. The extent of the cognitive impairment can be quite severe and impact substantially on the physical and mental well-being of cancer survivors. A subset of cancer patients appear to be more vulnerable. Patients receiving chemotherapy were found to be 2.25 times more likely to have cognitive decline after chemotherapy compared with a control group [172]. Up to 75% of breast cancer survivors can experience this during chemotherapy and it can persist for years after treatment in 20–35% of these women [96]. The mechanisms underpinning this cognitive decline are not well known.

There have been few studies that have investigated whether exercise can improve cognitive impairment associated with cancer and its treatment, though there are some currently underway [80, 86]. Exercise such as Chinese Tai Chi, a form of gentle exercise, has been shown to improve memory, attention and executive function in cancer survivors, as well as psychological and physical health [147].

Physical Activity and Urinary Incontinence Following Prostate Surgery

Incontinence is a side effect of prostate surgery for a substantial proportion of men with prostate cancer. A study of men post-prostatectomy found that men who were not obese and were active were 26% less likely to be incontinent than men who were obese and inactive. The study found that physical activity might confer some protection even in those men who were obese, since the prevalence of incontinence at 58 weeks was similar in the obese/active group and the non-obese/inactive group (25% vs. 24% incontinent) [188].

Reducing Risk of Co-morbid Disease in Childhood Cancer Survivors

Childhood cancer survivors have a higher risk of developing secondary cancers as well as other diseases [8]. Exercise plus diet interventions have been found to reduce the risk of co-morbid disease and prevent functional decline in childhood cancer survivors [53].

Exercise During Cancer Treatment

There is evidence of the benefits of exercise during and immediately following treatment for cancer. The American Cancer Society's (ACS) Expert Panel states that evidence strongly suggests that exercise is safe and feasible during cancer treatment and that it can improve physical functioning, fatigue and quality of life, can improve post-treatment adverse effects on bone health, muscle strength and quality of life and may also increase rate of completion of chemotherapy [150]. A systematic review of 14 studies of exercise in cancer patients reported that no adverse events were reported in 12 of the studies during the period of the exercise intervention. Of the other two that did report adverse events, in one study, a patient was nauseous, and in another study, three patients developed lymphedema, two of whom had had axillary radiation therapy (a risk factor for lymphedema) [146].

Whilst some studies have found that higher levels of activity and vigorous exercise confer more benefits [83, 109], in general regular (3–5 times per week for at least 20 min each session), low-moderate intensity physical activity involving aerobic, resistance or mixed type exercise is recommended by authorities such as the Australian Association for Exercise and Sports Science, for people undertaking or having completed cancer treatment [87].

The American Cancer Society and the Australian Association for Exercise and Sport Science recommend that decisions about when to begin and how to maintain physical activity should be individualised to the patient's condition and their preferences [87, 150].

Table 6.7 sets out some of the research findings in relation to exercise during various forms of cancer treatment.

Concerns About Acute Endurance Exercise in Relation to Cancer

There has been speculation in the past that acute endurance exercise might be detrimental in cancer sufferers because the endocrine effects of acute endurance exercise include increased levels of mitogenic factors such as Growth Hormone, increased cytokines such as IL-6 and increased bioavailability of IGF-1. The rationale would be that increased serum growth factors could promote progression of cancer into malignancy. However, a study found that when serum taken before (rest serum) and after 60 min of cycling exercise (exercise serum) was added to an established prostate cancer cell line, the exercise serum had a growth inhibitory effect and there was a 31% inhibition of the tumor cell line growth. The inhibitory effect on tumor cell growth was due to inhibition of proliferation rather than stimulation of apoptosis. When the exercise serum and rest serum were injected into mice injected with prostate tumor cells, the exercise serum caused a delay in tumor formation, suggesting a beneficial effect of endurance exercise [141, 155].

Table 6.7 Research on exercise during cancer treatment

Radiation therapy

In relation to radiation therapy:

- Combined aerobic and resistance exercise training over 4 weeks in prostate and breast cancer survivors undergoing radiation therapy significantly improved muscle strength, aerobic capacity as well as quality of life, sleep quality, CRF and immune function [131]
- Men with prostate cancer undergoing radiation therapy were randomised into an exercise group (moderate intensity home-based walking program for 30 min/day, 3 days/week over 10 weeks) or control group (advised to rest and take it easy if tired). Those in the exercise group had a significant improvement in physical functioning with no increase in fatigue, whereas those in the control group reported significant increases in fatigue [186]
- 121 men with prostate cancer receiving radiation therapy with or without ADT were randomly assigned to usual care, resistance exercise, or aerobic exercise for 24 weeks. Both forms of exercise were associated with reduced fatigue over the short term and resistance training was associated with longer term benefits including significant improvements in quality of life, aerobic fitness, upper and lower body strength and triglyerides [168]
- Men with prostate cancer undergoing radiation therapy who participated in a cardiovascular exercise program reported improvements in quality of life [130]
- A systematic review of prostate cancer survivors using androgen deprivation therapy (ADT), radiation therapy, or a combination of surgery and ADT found that there was strong evidence that exercise for a minimum of 2–3 days/week can significantly improve fatigue as well as physical fitness, functional performance and quality of life [104]

Chemotherapy

The American Cancer Society Expert Panel states that whilst the evidence is not clear on interaction between exercise and chemotherapy, there is evidence from one human study and an animal study that exercise did not interfere with chemotherapy [150]

In relation to chemotherapy:

- Results of an animal study indicated that moderate intensity exercise does not reduce the efficacy of chemotherapy [99].
- Exercise can be engaged in directly after high dose chemotherapy and can partially prevent loss of physical performance [49].
- Women with breast cancer assigned to a walking program (at least 90 min/week on 3 or more days) experienced significantly less fatigue and emotional distress and higher functional ability and quality of life than those assigned to the usual care group during adjuvant chemotherapy or radiation therapy [127]
- A small pilot study in 24 people with multiple myeloma receiving high-dose chemotherapy and autologous peripheral blood stem cell transplantation who undertook a home-based, individualised exercise program found it may be effective for decreasing fatigue and mood disturbance and improving sleep, however because of the small sample size, results were non-significant [34]
- 66 patients with blood cancer undergoing conventional or high-dose chemotherapy with stem cell rescue undertook exercise on a treadmill daily. Physical performance remained unchanged during hospitalisation and at discharge from baseline values [50]
- A meta-analysis of 28 studies, the majority carried out in breast cancer, concluded that exercise was beneficial for individuals with CRF during and after cancer therapy [45]

(continued)

Table 6.7 (continued)

Androgen deprivation therapy Side effects of Androgen Deprivation Therapy (ADT) due to its direct action on reducing testosterone production include reduction in muscular strength, less aerobic fitness, decreased functional performance, and changes in body composition and fatigue [104]. In relation to androgen deprivation therapy (ADT): • Regular exercise has been found to significantly improve quality of life, physical fitness, functional performance and quality of life in those on ADT, radiation therapy or a combination of ADT and surgery [104] • Men with prostate cancer who were undertaking ADT therapy were randomly assigned to an exercise group (resistance exercise program, three times per week for 12 weeks) or a waiting list control group. Those in the exercise group had significantly less interference from fatigue on daily activities and higher quality of life, and higher levels of upper and lower body muscular fitness than the control group [167]
Aromatase inhibitors Aromatase inhibitors are typically used to treat hormone-positive breast cancer to prevent recurrence, however they can have the side effects of joint pain and stiffness. In relation to aromatase inhibitors: • In postmenopausal women with hormone receptor positive breast cancer treated with aromatase inhibitors, which can cause joint pain, exercise was found to significantly reduce joint pain compared to women who didn't exercise [93]
Following surgery Exercise may be safe following surgery in particular cases • Breast cancer survivors who had completed treatment (except for hormonal therapy such as Tamoxifen or an aromatase inhibitor such as Anastrazole) 4–36 months prior to beginning the study were randomised into an immediate weight (resistance) training group (training from 0 to 12 months) or a delayed exercise (no training for 0–6 months, then training 7–12 months) group. Immediate resistance training was found to be safe and was associated with significant increase in muscle mass, and decreased body fat percentage and IGF-II [162] • Scar formation in joints as a result of radiation and chemotherapy may result in limitation in range of motion. Flexibility training may prevent this limitation and facilitate normal range of motion [146]
With lymphoedema In the past, there were concerns that those with arm lymphoedema should not engage in upper extremity resistance training or vigorous aerobic physical activity due to risks this would worsen it, however many clinical studies now demonstrate that it is safe and reduces the incidence and severity of painful lymphoedema that can occur following removal of lymph node with breast surgery [150] • Weight-training (twice per week over six months) did not increase the risk or increase the symptoms of lymphedema in breast cancer survivors with axillary dissection [3] • Twice-weekly progressive weight lifting conducted over one year had no significant effect on upper limb swelling and was associated with improved lymphedema symptoms, lower incidence of lymphedema exacerbations (as assessed by a certified lymphedema specialist), and greater upper and lower body strength in breast cancer survivors with stable upper arm lymphedema compared with the control group [164] • An RCT of 154 breast cancer survivors 1–5 years post-unilateral breast cancer, with ≥ 2 lymph nodes removed and without clinical signs of breast cancer-related lymphedema (BCRL) were randomised to a weight lifting intervention (gym membership and 13 weeks of supervised instruction, remaining 9 months unsupervised) or no exercise group. Significantly less (11%) women in the weight lifting group experienced incident BCRL onset compared to the control group (17%) in the 12-month study. In those with ≥ 5 lymph nodes removed, significantly less experienced incident BCRL onset in the weight lifting group compared with the control group (7% compared with 22%) [163]

(continued)

Table 6.7 (continued)

With bone metastases
Exercise has been perceived as a contraindication in prostate patients with bone metastases due to concerns about fragility fractures. Many of these patients experience functional impairment and muscle atrophy with attendant increased risks of fracture and bone pain and/or falls
• Twelve weeks of resistance exercise was found to be well tolerated in a small study of prostate cancer survivors with bone metastases, with no adverse events or skeletal complications occurring during the supervised exercise sessions. There was a significant improvement in physical function (approximately 11% improvement in muscle strength approximately 5% change in submaximal aerobic capacity), physical activity level (24%) and lean mass (approximately 3%) in the exercise group compared with the usual care group [38]

Exercise, Ageing and Cancer

Cancer incidence increases with age, with over 60% of new cancers and 70% of cancer mortality occurring in people 65 years or older [17]. A factor that may contribute to this is immune-senescence, the age-related decline in the functioning of the immune system including changes in the innate and adaptive systems [17]. This is important given the role of the immune system in dealing with cancerous changes in the body. It has been argued that there are many parallels between ageing and cancer. For example both are associated with decreased NK cell function [107]; a change that that can be reversed with exercise, and which has been shown to suppress tumor growth [141]. Ageing is also associated with decreased antigen presentation, which can lead to decreased cytotoxic T cell responses to new tumors, and chronic low-grade inflammation as a result of immune cell function changes with ageing contributes to a tumorogenic environment [17].

Regular exercise can prevent or even reverse many aspects of immunosenescence and therefore may help prevent cancer in the elderly as well as enhance treatment [17]. For example, regular aerobic and resistance exercise has been shown to increase NK cell cytotoxicity in older women [137] and can increase the number and activity of monocytes and macrophages including their anti-tumor cytotoxicity and production of tumor-inhibiting cytokines [191]. Exercise can also reduce inflammation that characterises the tumor microenvironment. Readers are referred to other sources for a comprehensive discussion on this topic [17].

Whatever the potential underpinning mechanisms, ageing is associated with a host of chronic illnesses including cancer, much of which is preventable through healthy lifestyle including a good diet and plenty of exercise. Thus, clinicians need to be talking with all of their patients (not just those presenting with cancer, but particularly those) about exercise.

Weight and Physical Activity Recommendations for Cancer Prevention

National cancer authorities have published recommendations in relation to weight and physical activity for the prevention of cancer. In general, the consensus is to reduce sedentary behaviour and incorporate regular physical activity as part of an individual's lifestyle, as usual activities (those done as part of daily routine) and as intentional (or planned) activities, and to aim for a healthy BMI [6].

The World Cancer Research Fund and American Institute for Cancer Research 2nd Expert Report recommends ensuring body weight throughout childhood and adolescent growth projects towards the lower end of the normal BMI range at age 21 and that people maintain body weight within the normal range thereafter, avoiding weight gain, and more importantly increases in waist circumference and abdominal fat on the basis that maintaining a healthy weight is one of the most important ways to protect against cancer and other chronic illness. In relation to physical activity, they recommend people limit sedentary activity (e.g. television watching), are moderately physically active, equivalent to brisk walking for at least 30 min per day or 150 min/week (which can be incorporated as occupational, transport, household, or leisure activities) and as fitness level increases, the aim

Table 6.8 American Cancer Society guidelines on nutrition and physical activity for cancer prevention

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention
On body weight 'Achieve and maintain a healthy weight throughout life • Be as lean as possible throughout life without being underweight • Avoid excess weight gain at all ages. For those who are overweight or obese, losing even a small amount of weight has health benefits and is a good place to start • Get regular physical activity and limit intake of high-calorie foods and drinks as keys to help maintain a healthy weight'
On physical activity 'Be physically active • Adults: Get at least 150 min of moderate intensity or 75 min of vigorous intensity activity each week (or a combination of these), preferably spread throughout the week • Children and teens: Get at least 1 h of moderate or vigorous intensity activity each day, with vigorous activity on at least 3 days each week • Limit sedentary behaviour such as sitting, lying down, watching TV, and other forms of screen-based entertainment • Doing some physical activity above usual activities, no matter what one's level of activity, can have many health benefits' [6; pp. 1, 2] • 'Adults should get at least 150 min per week of moderate intensity activity or 75 min per week of vigorous intensity activity, or an equal combination, in addition to normal activities of daily living. When combining different types of activity, 1 min of vigorous activity can take the place of 2 min of moderate activity. For example, 150 min of moderate activity, 75 min of vigorous activity, and a combination of 100 min of moderate activity plus 25 min of vigorous activity all count as the same amount' [6, p. 7]

Based on data from American Cancer Society [6]

should be $\geq$60 min of moderate or $\geq$30 min of more vigorous physical activity daily (physical activity of longer duration or greater intensity is more beneficial) [190]. The recommendations from the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention are set out in Table 6.8.

Considering the Important Social Aspects and Environmental Context of Exercising

Whilst there are compelling reasons why everyone who is able should exercise, and not just those with cancer, some attention needs to be given to the environment in which exercising takes place and well as the opportunities that exercise might bring for unloading of stored stresses. We have seen from Chap. 2 that social therapy plays a very important part in preventing recurrence and mortality from cancer, and the benefits of having a confidant. Exercising with a friend can be an important opportunity for unloading of stored stresses, with positive health benefits. And although the physical act of walking confers many benefits, some careful thought should be given to where one walks. Japanese research has shown that there are benefits to walking in the forest, as we can inhale beneficial substances when we breath forest air. These include beneficial bacteria, plant-derived essential oils and negatively charged ions (there is evidence that negative ions can positively affect mental outlook). Other places where there are high levels of negative ions are around large bodies of water like the ocean [44].

A meta-analysis of 10 studies that pooled data from 1252 participants found that exercising in natural environments was associated with significant improvements in mood and self-esteem, in those with and without a history of mental illness. Dose responses for both intensity and duration indicated benefits from short engagements in exercising in nature, with decreasing but still positive benefits. The presence of water generated greater effects [14].

Thus, where there are opportunities to get out and walk in nature or near the ocean, this should be encouraged.

Integrating Exercise in the Ultimate Consultation

It has been found that 70% of cancer patients and indeed almost all patients with a chronic disease receive no counselling about exercise during a normal medical consultation including its benefits during their cancer treatment [52, 77]. The oncologist is in a unique position to advise the patient about the benefits. Since barriers to doctors promoting exercise is often lack of exercise-specific knowledge, bringing an exercise physiologist into the team of practitioners assisting the patient would seem to be a practical solution [77].

Discussing Physical Activity

The American Cancer Society recommended that individuals avoid inactivity and return to normal activity as soon as possible after diagnosis or treatment [150]. As discussed previously, there is evidence that exercise is safe and feasible during cancer treatment, however it is important to recognise that some types of exercise may be contraindicated in specific instances, e.g., high impact activities or heavy strength training in cancer patients with bone metastasises or ataxia or high intensity exercise during a secondary infection [87].

In the Ultimate Consultation, the clinician should incorporate discussion of physical activity including the patient's medical and exercise history, any exercise contraindications to exercise, especially possible signs of cardiac or uncontrolled metabolic disease, musculoskeletal complications or recent surgeries, and their exercise likes and dislikes. The clinician can also share some of the research evidence demonstrating that physical activity is beneficial in improving cancer prognosis and general health and well-being, and where relevant, how exercise may reduce adverse symptoms of chemotherapy or radiotherapy.

Referring to Accredited Exercise Physiologists

There are several recommendations and precautions to take into account, in particular for planning exercise during treatment. Oncologists, doctors and many other healthcare professionals who are assisting people with cancer often do not have the expertise, beyond the basics (and sometimes not even those), to advise on exercise and set up an exercise program. A referral to an accredited exercise physiologist should be recommended. Exercise physiologists are allied health practitioners who are highly trained in all aspects of clinical exercise physiology and prescribing exercise to optimise specific health outcomes. Exercise physiologists are increasingly trained in the specialty area of cancer management, and have the qualifications and experience to tailor an exercise program for the cancer patient. Such a program is individualised, taking into account all aspects of the patient's medical history, type of cancer, other relevant chronic diseases and co-morbidities, relevant musculoskeletal considerations, pre-diagnosis level of exercise, cancer treatment and its likely side effects, any exercise contraindications and exercise likes and dislikes to maximise exercise compliance. The exercise physiologist can then instruct and supervise the client, in at least the initial stages of the exercise program, to ensure good exercise form, assist with compliance, provide some ongoing education about the benefits of exercise and monitor any adverse signs or symptoms, such as any pain, increased fatigue or nausea.

In Australia, a Medicare Chronic Disease Management Plan can be developed which provides a rebate of up to five exercise physiology consultations per year. The following website may be consulted to find an accredited exercise physiologist in Australia: https://www.essa.org.au/find-aep/.

Identifying the Patient's Exercise History and Likes/Dislikes

In the Ultimate Consultation, the clinician in collaboration with the exercise physiologist should discuss the level and types of physical activity the patient is currently engaging in, as well as in their recent and not so recent past. Those who are used to exercising are more likely to be in the *habit* of exercising. Regular or habitual exercise is an important part of an integrated Wellness Plan.

Inquiring about what exercises the patient enjoys in particular can then lead into some recommendations about incorporating such forms of exercise into daily life. Patients are more likely to engage in exercise that is enjoyable to them. Whilst there are clearly benefits for a number of forms of exercise, for example yoga or tai chi, some may be a bit more of a stretch (metaphorically) than others, if the patient has never practised such forms before. However, most people are able to walk and walking, particularly brisk walking as we have seen earlier, is a particularly beneficial form of exercise. Walking doesn't require special equipment other than a decent pair of walking shoes and comfortable clothing, unlike some other forms of exercise.

Many people will prefer to exercise at a particular time of day. Some people are 'owls' (late–to-bed, late-to-rise) and others are 'fowls' (early to bed, early to rise) in terms of their biorhythms, so this needs to be considered. There's no point in trying to convince a late-to-bed and late-to-rise person to get up early to exercise when they hate getting out of bed early.

The excuse that there isn't enough time to exercise is put to bed, metaphorically, by research that has found that a minute of very intense exercise (1 min of sprint training within a 10 min-time commitment) produces cardio-metabolic health benefits similar to 50 min of traditional, moderate intensity continuous endurance training over 12 weeks (three weekly sessions) [78]. However, in the case of cancer patients, low-moderate intensity exercise is generally recommended. The point here is that small amounts of exercise may be still beneficial.

Resistance training, aerobic exercise and flexibility training are all beneficial, and again it will be important to identify with the patient what forms of exercise will produce the best health outcomes for them, will minimise any complications and will be interesting and practical for them to continue in the longer term.

Group exercise or home-based exercise or both?

Group and home-based exercise has been found to provide significant improvements in quality of life, general well-being, physical fitness and functional performance in older cancer survivors and breast cancer survivors [27, 42, 60, 61, 144]. Group exercise was found to be more effective than home-based exercise in one study of prostate survivors in terms of providing health benefits, some instruction and supervision and improving exercise compliance [104]. Group exercise classes involving other people living with cancer have the benefits of providing a social atmosphere, a chance to share stories and concerns about the experience of living with cancer and importantly unload stress. The disadvantage or conversely, perhaps an advantage, of group or supervised classes is that the person

may need to travel to a gym or other venue to participate in. This can sometimes be difficult for those without their own transport (in particular those who may not be confident using public transport) or older clients. On the flip-side, it provides a change of environment, social support from friends or others going though similar health challenges and perhaps some time out from well-meaning family which might be important.

Exercise and social therapy

Home-based exercise also offers the opportunity for partners and other support persons to participate with the cancer patient, for example walking together. In many cases this can have several added benefits, for example it demonstrates support for the person with cancer, provides important opportunities for the patient to unload stress, and provides health benefits for the support person themselves. People who support those living with cancer are usually also under significant stress themselves, and can often be forgotten. However, it is also worth considering that the partner may be a large part of the stress of the cancer patient's life and exercise alone or with a support group might just be a welcome break from it all.

Home-based or group-based physical activity does not have to be an either/or choice. Perhaps both, if doable, might be advantageous. Discuss the options with the patient, and have on hand a referral list of exercise venues or classes that are geared to cancer survivors, plus exercise physiologists who may be able to assist in the creation of an individualised exercise program. If you don't have exercise physiologists as part of your referral network, for Australian healthcare practitioners, Exercise and Sports Science Australia has a list of accredited exercise physiologists on its website (https://www.essa.org.au/find-aep/).

Key Points

- Keep a handy referral list of exercise venues or classes that are geared to cancer survivors
- Make accredited exercise physiologists part of your referral network.

Exercise Goal Setting Including Lifelong Goals for Living With and Beyond Cancer

In general, for everyone and not just those with cancer, accumulation of exercise is the key and by being flexible in how exercise is scheduled, exercise goals are achievable, whatever these may be. Again, in general, exercise can be undertaken whenever it suits the patient, with the goal of undertaking enjoyable physical activities. Ideally planned aerobic, strength (anaerobic) and flexibility exercise

should be incorporated into a Wellness Plan and this can be assisted and supervised by an accredited exercise physiologist.

However, whilst planned exercise is important, it is also very beneficial to incorporate incidental exercise into daily life as much as possible and reduce the amount of time sitting, with the goal to reduce sedentary behaviour. Examples of incidental exercise would be walking up the stairs instead of taking the elevator at work, or parking a bit further and walking to work. Thus in exercise goal setting with patients, clinicians can discuss ways to increase forms of incidental exercise.

Key Point

- In setting an exercise goal with patients, clinicians should discuss incidental exercise as well as planned exercise.

Principles for Incorporation of Exercise into Wellness Plans

The following principles may be taken into account when setting exercise goals for cancer survivors, based on those from the *Nutrition and Physical Activity Guidelines for Cancer Survivors* [150] and the *American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors* [163]:

1. Recommendations for physical activity set out in the *2008 US Department of Health and Human Services (US DHHS) Physical Activity Guidelines for Americans* (see Table 6.9), are considered generally appropriate for cancer survivors by the American College of Sports Medicine (ACSM) Expert Panel, recognising that modifications may need to be made based on health status, treatments and disease trajectory
2. Some activity is better than none and that cancer survivors should engage in regular activity and avoid inactivity and return to normal physical activity as soon as they can after diagnosis, during adjuvant cancer treatment and after surgery [150].

Table 6.9 US Department of Health and Human Services (US DHHS) physical activity guidelines for Americans

1. Aerobic exercise: an overall volume of weekly activity of 150 min of moderate-intensity exercise or 75 min of vigorous-intensity exercise or an equivalent combination
2. Strength training: perform two to three weekly sessions that include exercises for major muscle groups
3. Flexibility training: stretch major muscle groups and tendons on days that other exercises are performed [165]

3. Cancer survivors should aim to achieve and maintain a healthy weight and reduce abdominal fat levels, and that if overweight or obese, increase physical activity to promote weight loss and seek dietary advice to limit energy intake especially of high-calorie foods/drinks, and foods high in saturated fat [150].
4. Exercise programs should be individualised according to the individual's pre-diagnosis and pre-treatment fitness level, medical co-morbidities, diagnosis, treatments and response to treatments (many of which are associated with side effects and toxicities including neuropathies, increased risk of fractures and cardiovascular events) [87].
5. Certain precautions (Table 6.10) should be heeded in designing exercise programs for cancer survivors, as recommended by the *American Cancer Society Expert Panel* and the *American College of Sports Medicine Roundtable of Cancer*.
6. Recommendations for modifying exercise plans for particular cancers are set out in the *American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors* [163].
7. Ways to incorporate incidental exercise as well as planned exercise should not be forgotten.
8. Behavioural change is not easy and should be supported.

Table 6.10 sets out guidelines that may be considered in relation to exercise programs for cancer survivors, based on recommendations set out in the American Cancer Society's *Nutrition and Physical Activity Guidelines for Cancer Survivors* [150] and the *American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors* [165]. The Exercise and Sports Science Australia Position Statement 'Optimising Cancer Outcomes Through Exercise', also provides an excellent resource for clinicians when making recommendations to cancer patients on exercise (aerobic and resistance-based exercise) during and following cancer treatment [87].

Table 6.10 Recommendations for exercise planning for people with cancer

• Those Already On Exercise Programs: Those receiving chemotherapy and/or radiation therapy who are already on an exercise program may need to lower the intensity or shorten the duration of training during treatment, however the goal should be to maintain as much physical activity as possible [150]
• Those Who Were Sedentary Pre-Diagnosis: Those who were sedentary before diagnosis should introduce and slowly increase low-intensity physical activity, e.g. stretching and brief slow walks [150]
• Start Gently Where There is Fatigue: If a patient is experiencing severe fatigue from their therapy, they may not feel like exercising, however they may be encouraged to do 10 min of light exercises daily [150]. Exercise tolerance of patients currently in treatment and immediately after treatment may vary from exercise session to session, depending on their treatment schedule [165]
• Wait to Determine Side Effects of Chemotherapy: it may be advisable in the case of some individuals to wait to determine the extent of chemotherapy side effects before beginning physical exercise [150]

(continued)

Table 6.10 (continued)

• During Bed Rest: Where bed rest is necessitated, physical activity during bed rest is advised to maintain strength and range of motion and counteract fatigue and depression [150]
• Older People: Care should be given to balance and safety in older cancer survivors and those with bone metastases or osteoporosis or significant impairments, e.g. peripheral neuropathy, arthritis to reduce risk of falls or injuries [165]
• With Co-Morbidities: where there are multiple or uncontrolled co-morbidities, exercise programs may need to be altered [150]. Those with heart conditions (secondary to cancer or not) will require modifications to their exercise program and may need additional supervision for safety ([165] ACSM)
• With Peripheral Neuropathy or Ataxia: those with significant peripheral neuropathies or ataxia may have a reduced ability to use affected limbs because of weakness or loss of balance. A stationary reclining bicycle may be a better option that walking on a treadmill [150]
• With Metastatic Disease: will require modifications and supervision to avoid fractures Those with bone metastases may need to alter the intensity, duration and mode of an exercise program given increased risk for skeletal fractures [165]
• With Anaemia: if anaemia is severe, exercise should be delayed other than activities of daily living, until the anaemia is improved [150]
• Where Immuno-Compromised: Infection risk is higher for patients undergoing chemotherapy or radiation therapy or those who have compromised immune function after treatment [166]. Cancer survivors with compromised immune function are advised to avoid public fitness centres and pools until their white blood cell counts return to safe levels. Those who have had a bone marrow transplant are usually advised to avoid such exposures for one year after transplantation [150]
• While Undergoing Radiation Therapy: Those undergoing radiation therapy are advised to avoid chlorine exposure from, for example swimming pools, to irradiated skin [150]
• With Indwelling Catheters or Feeding Tubes: Those with indwelling catheters or feeding tubes should also be cautious or avoid pool, lake, ocean water or other microbial exposures that may result in infections. They should also be cautious or avoid resistance training of muscles in the area of the catheter to avoid dislodgment [150]

Based on data from: [165, 150]

Supporting Behavioural Change

Several studies have suggested that cancer survivors do not engage in sufficient physical activity. Evidence suggests that less than 10% of cancer survivors are likely to engage in physical activity during treatment [150]. NHIS data (1998–2001) indicated that approximately 30% of cancer patients met the CDC/ACSM physical activity guidelines compared with 37% without a history of cancer [16]. In Australian men with prostate cancer only 12.3% reported a sufficient level of exercise (150 min of moderate intensity or 75 min of strenuous exercise per week and twice-weekly resistance exercise) whilst 40.2% were insufficiently active and 47.5% were inactive [72].

The reasons why cancer survivors don't engage in sufficient physical exercise are likely to be complex. Prevalence of strength exercise was found to be low among prostate, breast and colorectal cancer survivors, and those who were younger, more

educated, with a higher income, better perceived health, healthy body weight, less than two co-morbidities and who had greater intention were more likely to meet the recommended strength exercise guidelines at least two days per week [64]. A study in survivors of cancer under the age of 18 years found that common barriers to exercise were being too tired or busy, not belonging to a gym, or preferring to do other activities such as watch television, read a book or use a computer [8].

Reinforcing Physical Activity Goals

Incorporating physical exercise into lifestyle, particularly when there hasn't been a past history of much physical exercise, may be a challenge to the cancer patient and it will require discipline. It is Professor Sali's experience that people who have been professional sportsmen or sportswomen are able to change their habits more easily (this includes diet and not just physical activity) as they are used to the discipline of training.

To get the Ultimate Result, the clinician needs to spend time with the patient to motivate and set goals for the exercise program and to consider any barriers that might prevent them engaging in an exercise program. The medical practitioner and/or the exercise physiologist can assist the patient by reinforcing physical activity goals as part of the individualised Wellness Plan and/or through the patient's health care plan. Patients can be encouraged to keep a diary (though this is not everyone's cup of tea) to record their experiences, achievement of goals and impact of exercise on their overall well-being, as a way of charting their progress and motivating them to continue with their exercise program.

Behavioural Change Support

Behavioural change may need to be supported. The clinician may also enlist the support of other health professionals to support patients through the initial stages of an exercise program, to assist them overcome any of the identified barriers (e.g. fear of adverse effects associated with exercise), that may prevent them getting started or continuing in the longer term. Thus, behavioural support interventions such as short-term supervised exercise programs, support groups, cancer-survivor-specific print materials and telephone counselling [150] may also be important to assist cancer survivors to adopt and maintain physically active lifestyles. Such interventions may need to be modified for children, particular in the age of technology where we are already facing an epidemic of sedentary behaviour, enabled by the obsession with hand-held devices. Perhaps there may be an opening for development of exercise Apps aimed at different age groups for cancer survivors.

The ultimate goal will be to incorporate exercise as a way of life, in particular for those who are not used to exercising.

Key Points About Exercise in the Ultimate Consultation

- Incorporate discussion about the benefits of physical activity on health outcomes in cancer
- Identify the patient's exercise history and likes/dislikes
- Set some exercise goals including lifelong goals for living with and beyond cancer
- Suggest the patient keeps an exercise diary
- Behavioural change is difficult and may require support from other health practitioners

Some Examples of Physical Activities

There are several different kinds of physical activities that might be of interest to patients living with cancer, as well as their support persons. There is a growing evidence base around the positive impact that many of these can have in patients with cancer. Let's look at a few different forms of exercise that you as the clinician might be able to suggest.

Aerobic Exercise

Exercise is aerobic when it is sustained for at least 10 min and is of submaximal intensity.

There are many forms of aerobic exercise. One of the easiest, of course, is simply fast walking—it doesn't require any fancy equipment other than some decent walking shoes, and importantly if done during the day, gets the patient out in the sunshine and helps them get a daily dose of Vitamin D, and can involve social support if done with a friend.

Generally, light to moderate intensity exercise (that which gets your heart rate elevated with some mild 'puffing' but where you can still talk) is appropriate. Some additional examples of light to moderate intensity exercise include the following: swimming or water aerobics, and other aquatic activities, ballroom dancing, line dancing, stationary or cycling on level ground (as long as there is no evidence of poor balance), general gardening (raking, trimming shrubs), golf, and walking briskly [150]. By way of contrast, more vigorous aerobic activities are those that elevate the heart rate more than moderate intensity activities and are generally those activities in which you can only say a few words without stopping to catch your breath [150].

Resistance or Strength Training

Resistance or strength training involves short intense bursts of movement against resistance, usually in the form of weights or body weight, resistance bands or using resistance machines. Typically, the number of repetitions is 8–15 or less (this is called a 'set'), and the amount of weight or resistance is set so that this can be just achieved. If the patient can do more than 12 repetitions, then the amount of resistance should be increased [57].

Generally, three sets of each exercise, with a 30–90 s recovery period between each set, provides a good stimulant to increase muscle strength. A resistance training session includes 8–10 different strength training exercises which stress the major muscles of the legs, upper back, chest, shoulders, arms and importantly the core muscles of the abdominal wall. The specific exercises selected should be based on the client's pathology including any musculoskeletal pathology or injury concerns, the clinical priorities of the client, and the exercises should also incorporate multi-joint functional movements, which improve strength to undertake daily activities. In general, the patient should complete 2–3 resistance training sessions per week, on alternate days to give the muscles time to regenerate and become stronger as a result of repeated sessions [57]. As the body adapts to the training load, training is progressively increased by increasing resistance, reducing the time between sets or changing the exercise difficulty or sequence.

Resistance training can be done in the home or at a gym, under the supervision of an exercise accredited physiologist or exercise scientist. It is worthwhile for the patient to be given instruction in the correct technique to complete resistance training exercises to monitor any adverse symptoms or pain and to provide guidelines on appropriate progressive overload for each client to get the most out of the exercise program and to avoid injury.

Flexibility Training

Joint and muscle flexibility can diminish with age. Flexibility (stretching) exercises help lengthen muscles and tendons, and improve and maintain joint mobility and stability and the strength of muscles, so as to reduce the likelihood of injury. Ideally, flexibility exercises should be incorporated 3–4 times per week. Examples of flexibility or stretching exercises can also be found in the (Australian) Cancer Council's publication Exercise for People Living with Cancer [30] or in exercise physiology texts [57].

Tai Qi and Qi Gong

Tai chi and qi gong are forms of Chinese exercise therapy that have been practised for hundreds of years. Whilst appearing rather gentle forms of exercise, utilising lower and upper limbs with flowing series of body movements, they nonetheless are beneficial in terms of developing lower body muscles in particular since the exercises are done very slowly and deliberately, requiring muscle control, balance and strength. The aim of both forms of exercise is to facilitate the flow of Qi, a form of subtle energy, around the body. Qi is believed to circulate within the blood as well as through special pathways in the body called 'meridians'. Where the flow of qi is blocked, it can cause pain. Where the flow of qi is not smooth, emotions are not regulated and depression and moodiness can result.

There is some limited research that tai chi may cause beneficial changes in immune functioning. For example, a 6-month tai chi program was found to be associated with significantly improved immune functioning in middle aged and elderly females, with changes in Th1 and Th2 immune responses possibly associated with the immune modulation of Natural Killer T cells and Dendritic Cells and their reciprocal interactions [111]. A 16 week tai chi program in patients with non-small cell lung cancer was associated with enhanced peripheral blood mononuclear cells (PBMC) proliferative and cytolytic activities [112]. There is also evidence that tai chi is efficacious in reducing insomnia, which may also be beneficial in cancer survivors given that sleep problems are particularly prevalent in this group, as well as preventing falls in older persons [136]. A systematic review of complementary medicine therapies for the treatment of chronic insomnia found evidence that tai chi was efficacious [158].

Yoga

Yoga combines flexibility training with resistance training and in some forms, aerobic training. There are many forms of yoga. Whilst most of them combine the achievement of physical postures, termed asanas, with breath-work and meditation, the emphasis placed on each of these varies between yoga types or schools and between teachers. For example, some focus in particular on achievement of the physical postures. In Iyengar Yoga the aim is to achieve a particular posture, hold it, then return to a neutral position, whilst in other types of yoga, one posture flows into another, so there is continual movement. Other forms of yoga focus more on breathing and meditation, and these may assist with stress reduction and general mood. An experienced yoga teacher who can instruct on correct physical postures is essential to avoid strain and injury.

There is a plethora of research on the benefits of yoga on stress reduction. There is also evidence from a systematic review that it is efficacious is treating chronic insomnia [158]. There is also some research into the benefits of yoga in cancer. For example, women with non-metastatic breast cancer who participated in an 8-week program of

twice-weekly yoga exercise were significantly less fatigued and had reduced interference of fatigue with daily life compared with women who received standard care only, though the study did not find a significant change in depression [176].

Climb for Life

There are some innovative physical activity events that challenge people physically and at the same time, help educate and raise awareness. One such event is 'Climb For Life' which is held in various cities in the United States. The events allow women to learn about ovarian cancer and at the same time, gain physical and mental benefits from rock climbing as a sport. The program has expanded to include trekking and other health promoting physical activities. For more information, see www.heartfoundation.org.

Specific Exercises for Supporting the Bladder and Bowel

Many cancer survivors will suffer the problems associated with weak pelvic floor muscles, for example, following pelvic or abdominal surgery or prostate surgery. Weak pelvic floor muscles can lead to incontinence when the patient coughs, sneezes, laughs or lifts heavy objects. Physiotherapists and continence advisors can instruct patients in how to correctly perform pelvic floor exercises to strengthen these muscles.

Conclusion

Research is rapidly accumulating on the importance of regular low-moderate intensity exercise in prevention of chronic disease [75] and in particular its role in the prevention of range of cancers and as a critical adjunct therapy in the management and treatment of cancer. Exercise has recently been shown to be as effective as many pharmacological interventions in the treatment of chronic disease [77] and its role in an integrated Wellness Plan for cancer management is now undeniable. There is clear evidence that a sedentary lifestyle is dangerous to health, is a causative agent in cancer, and that exercise is able to reduce the risk of developing cancer as well as reduce the risk of dying from cancer or other causes of death. Exercise can also alleviate many of the associated signs and symptoms that may accompany cancer and cancer treatment.

Physical activity can assist in weight loss in those who are overweight or obese, but it has anti-tumor actions [141] and other health and psychological benefits independent of this. There is now evidence that exercise is beneficial, safe and

feasible during cancer treatment, as well as after treatment, taking into account some specific precautions in relation to particular kinds of cancers and treatments.

Exercise is not often discussed with the cancer patient, and it needs to be, as there are very clear health benefits. It is one of the essential topics for discussion in the Ultimate Consultation.

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Chapter 7
Additional Therapies and Innovative Technologies

In this chapter we explore:

- Dietary supplements including vitamins and herbs that can assist in cancer.
- A basic list of supplements and a supplementary list that can be prescribed.
- High dose, intravenous vitamin and herbal therapy.
- Chinese herbal medicine and acupuncture.
- Innovative diagnostic technologies and treatment therapies including circulating tumor cell (CTC) tests, hyperthermia, photosonodynamic therapy (PSDT) and immunotherapy with Gc-MAF.

Introduction

There is a need to look beyond what conventional cancer treatments offers. In addition to stress reduction techniques, nutrition, good sleep, sunlight (and Vitamin D) and physical exercise, there are several complementary therapies that can be integrated with orthodox cancer care. These include vitamins, trace elements, western herbal supplements, high dose, intravenous vitamin therapy, and Chinese herbal medicine, acupuncture, and some of the innovative therapies.

Most doctors and oncologists are not trained in nutritional medicine or forms of complementary medicine, though this is changing with the introduction of Integrative Medicine as a clinical specialty of medicine in the US (other countries are likely to follow suit in the future). However, it is difficult to be an expert in every field. An integrated care approach to assisting people living with cancer involves a team of professionals, each with their own expertise.

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In This Chapter

This chapter will address the last two of the Seven Key Health Strategies outlined in Chap. 1. It will present some of the scientific evidence in relation to several complementary medicines including dietary supplements, western herbs, high dose intravenous vitamin therapy, Chinese herbal medicine, and acupuncture. It will also explore some of the innovative investigative technologies and treatment therapies including the use of circulating tumor cell testing, hyperthermia, photosonodynamic therapy, and immunotherapy with GcMAF.

Basic Dietary Supplements

Vitamin and other dietary supplements are often useful, in particular where diet may be inadequate. For a variety of reasons, the nutritional value of foods is often deficient. Also, when a person doesn't have a sufficient variety of foods, in particular vegetables in their diet, it is not difficult to see that they could become deficient in vitamins and trace elements.

Adequate micronutrients are essential for the immune system to function properly and deficiency suppresses immunity, thereby increasing susceptibility to infections [156]. Vitamins A, C, E and trace element zinc enhance skin barrier function, and Vitamins A, B6, B12, C, D, E and folic acid and trace elements iron, zinc, copper and selenium support the activities of the immune system and are needed for the production of antibodies. Taking a multivitamin with trace elements was found to significantly decrease the rate of infections and nutritional deficiencies and improve immune functioning in healthy elderly adults living independently [38].

One large study (the Physician's Health Study) also found a modest decrease in overall cancer risk in men who took a multivitamin supplement prior to cancer diagnosis [78], however in general, authorities such as the World Cancer Research Fund International do not recommend dietary supplements for the prevention of cancer [270].

The usefulness of any dietary supplement is not about cancer prevention per se, but ensuring that the person is as healthy as possible where dietary sources of vitamins and minerals might be deficient (with or without cancer).

Table 7.1 sets out a list of basic supplements that Professor Sali prescribes for most cancer patients. The dosages may need to be adjusted, based on the individual, however it is provided as a guide. Some of the evidence in relation to each of these supplements is set out in the following pages.

Multivitamin Supplements

A good quality multi-vitamin tablet which contains trace elements is recommended to be taken daily (all the trace elements are needed for proper immune functioning).

Table 7.1 Basic supplement list

Supplement	Recommended dose (see notes on individual supplements)
Multi-vitamin including trace elements	1 tablet daily or as directed on packaging
Vitamin D3	When a patient has low Vitamin D levels [<75 mg]: High dose (10,000 IU) daily of Vit D3 for 2–3 weeks then thereafter, a lower dose which is dependent on the season: Winter: 3 × 1000 IU Vit D3 daily Summer: 1000 IU Vit D3 daily is generally sufficient if there is sun exposure Vitamin D measurement is essential to ensure correct dosage
Vitamin C	1000 mg twice daily or more if no bowel looseness
Vitamin E	A complete Vit E which contains both the tocopheroals and toctrienols is recommended. Dosage varies, however normally a standard capsule twice daily
Selenium if there is evidence of blood stickiness, otherwise optional	100–200 μg/day (depending on nutritional status) (2–4 tablets daily of 50 micrograms each)
Fish oils	1.8 g twice daily (EPA 720 mg, DHA 480 mg) During chemotherapy take 2 x 1.8 g twice daily
Probiotics	A probiotic tablet containing 25–50 billion microbes per capsule taken last thing at night Patients on chemotherapy: use a higher dose probiotic during chemotherapy: 50–100 billion microbes per capsule

Recommended Dose:

- 1 tablet daily

Vitamin C Supplements

Many cancer patients are significantly depleted of ascorbate which might suggest an increased requirement of this vitamin to potentiate the various defence mechanisms associated with this vitamin [80]. Vitamin C plays a strong role in the body's defence system and plays a vital role in both humoral and cell-mediated immunity. Ascorbate is essential for immunoglobulin synthesis. Lymphocytes contain high concentrations of ascorbate, and ascorbate is also necessary for phagocytosis and enhances interferon production [80]. Vitamin C is known to be a strong reductant and scavenger of free radicals and is able to protect cells against reactive oxygen species (ROS) generated during the inflammatory response [184, 268]. Supplementation with Vitamin C has been found to improve antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity [268].

Linus Pauling's 1971 study compared 100 terminally ill cancer patients given 10 g of Vitamin C daily with 1000 terminally ill cancer patients who acted as the

control. The protocol was intravenous (IV) infusion for the first 10 days and oral supplementation thereafter. The results indicated that for about 90% of the treatment group, deaths occurred at one third of the rate as that of the controls, representing a three-fold increase in survival time. In about 10% of the treatment group, survival was increased by at least 20-fold [31]. When they analysed the data a few years later, the treatment group was found to have a mean survival time of about 300 days greater than the control group. Survival times were observed to be greater than a year following date of 'untreatability' in 22 of the treatment group (22%) compared with 4 of the 1000 controls (0.4%), with a mean survival time in these 22 people of 2.4 years after reaching terminal stage [32]. These findings confirmed the earlier data which indicated the benefits of Vitamin C supplementation in terminally ill patients. Other randomised controlled trials, however, have not found benefit of oral supplementation with Vitamin C in patients with advanced cancer [52] and colorectal cancer [172].

There is evidence that high doses of Vitamin C, typically achieved by intravenous (IV) administration is particularly effective against cancer. This is discussed in a later section on IV Vitamins.

Recommended Oral Dose:

- Vitamin C: 1000 mg twice daily or more if no bowel looseness

Vitamin D Supplements

Vitamin D profoundly affects the body. As discussed in Chap. 5, there are Vitamin D receptors all over the body, indicating its far-ranging effects. Sunshine exposure is the best way to get sufficient Vitamin D, however many people are deficient in this vitamin due to modern life habits of working inside during the daylight hours. In Professor Sali's experience, he has never had a cancer patient with normal vitamin D levels, He considers a normal vitamin D level to be >75 mg, but it is even better, in his opinion, if their level is over 100 mg.

Recommended Dose (when a patient has low Vitamin D [<75 mg]):

- High dose (10,000 IU) daily of Vit D3 for 2–3 weeks then thereafter, a lower dose which is dependent on the season
- Maintenance Dose
- Winter: 3 × 1000 IU Vit D3 daily
- Summer: 1000 IU Vit D3 daily is generally sufficient if there is sun exposure

Re-measure Vitamin D levels in 3 months.

These are guidelines only and what is prescribed depends on the individual as well as the season of the year.

Vitamin E Supplements

Vitamin E is a family of eight different isomers including tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol) and tocotrienol forms (four of these) [48]. All members of the family of naturally occurring Vitamin E isomers are antioxidant compounds that derive their redox or antioxidant capacity from a hydroxyl group at the C6 position on the chromanol ring. Synthetic versions of Vitamin E (analogues) which are popularly used in nutritional supplements (as they are more stable) have lost the hydroxyl group and have a substitution at the C6 position with an ester linkage of either acetate or succinate [113]. An important point to note is that these analogues do not have any antioxidant capacity [113].

Dr. Roy Bean found, in the 1950s, that cancer patients have 'sticky blood', that is they have a greater propensity to suffer from deep vein thrombosis (DVT), stroke and heart attacks. Vitamin E has been found to decrease platelet aggregation [71, 215, 236], and therefore can help normalise platelets and blood stickiness. Moderate to high levels of homocysteine, a marker of inflammation, in healthy adults was found to activate coagulation, modify the adhesive properties of the endothelium and impair vascular responses to L-arginine, however pre-treatment with Vitamin E and Vitamin C was able to block this increase in homocysteine [183].

Unfortunately, the term 'Vitamin E' is used to refer to the both the naturally occurring and the synthetic versions (analogues). This is likely to have led to some confusion in the literature about the efficacy of the various forms of Vitamin E. Research often fails to distinguish between the redox-sensitive tocopherols/tocotrienols and the redox-silent (no antioxidant capacity) synthetic analogues such as dl-alpha tocopheryl succinate (aTOS) which shows promise as an anti-cancer agent [113]. Synthetic analogues have their own biological activities. Research has demonstrated that the different iso-forms may have opposing effects within the body, and variations in reports on the outcomes of Vitamin E treatments (both in vitro and in vivo) may be due to differences in isoforms and the purity of the tocopherols, as well as differences in concentrations of the tocopherorols in different cells and experimental systems [48].

γ-tocopherol

Whilst the majority of research has tended to focus on α-tocopherol which is the primary form of Vitamin E in supplements and in human tissue and plasma (and has higher bioavailability and bioactivity), it is γ-tocopherol that is the major form of Vitamin E in many plant seeds and in the American diet and it has unique features that may be important for human health. γ-tocopherol constitutes 30–50% of the total vitamin E in human skin, muscle, vein, and adipose tissue and the concentrations in these tissues is 20–40 times greater than those in plasma [28]. The metabolite of γ-tocopherol, 2,7,8-trimethyl-2-(β-carboxyethyl)-6-hydroxychroman (γ-CEHC), but not the equivalent metabolite of α-tocopherol, has natriuretic activity of importance for physiological functioning [111]. γ-tocopherol and its

metabolite but not α-tocopherol inhibit cyclooxygenase and are therefore anti-inflammatory [111].

Whilst human studies of supplementation with α-tocopherol have not found firm evidence of a protective effect of α-tocopherol on cardiovascular disease [93, 111, 159], there is evidence that γ-tocopherol may be protective [127]. Plasma concentrations of γ-tocopherol have been found to be inversely associated with cardiovascular disease [190] and prostate cancer incidence [91].

An important point to note is that high doses of α-tocopherol supplementation deplete plasma and tissue γ-tocopherol [87, 88] whereas supplementation with γ-tocopherol in Vitamin E-deficient rats increases the concentration of both α-tocopherol and γ-tocopherol in nervous tissue, heart, liver and muscle [46].

γ-tocotrienol

A recent study that investigated the in vitro and in vivo effects of γ-tocotrienol found that γ-tocotrienol inhibited the proliferation of colorectal cells with wild-type or mutated KRAS, and it also induced apoptosis, inhibited colony formation, and suppressed key regulators involved in the pathways involved in cancer (including those involved in cell survival, proliferation, invasion, angiogenesis and metastasis). In combination with the chemotherapeutic agent capecitabine, it was found to enhance the drug's effect in colorectal cells. In mice experiments, γ-tocotrienol was found to inhibit tumor growth and enhance capecitabine's anti-tumor effect. The combination of the γ-tocotrienol and capecitabine down-regulated NK-κB and gene products regulated by it, and inhibited a range of other factors involved in cancer including vascular endothelial growth factor (VEGF) [198].

Interpretation of research

Vitamin E research needs to be interpreted carefully and consideration given to results in light of the isomer investigated, as well as whether a synthetic or natural version has been used. For example, the SELECT Study found in that in healthy men who took 400 IU of synthetic Vitamin E daily for 5.5 years, there were 17% greater risk of prostate cancer compared to men taking placebos [125]. There are a number of possible explanations, including the possibility that the daily dose was too high—there may be a U-shaped dose-response curve [180]. In addition, in this study the analogue alpha tocopherol *acetate* (aTOA) was used, and synthetic Vitamin E is known to deplete the γ-isoform of Vitamin E [88] which is protective against prostate cancer [91]. Conversely, in the Alpha-Tocopherol Beta Carotene (ATBC) Cancer Prevention trial there was a 32% decreased incidence of prostate cancer in male smokers who took 50 IU daily of α-tocopherol (a much lower dose that the SELECT Study), and mortality was 41% lower [90].

Another study in head and neck cancer found that a combination of α-tocopherol (400 IU of *dl*-α-tocopherol) and β-carotene (30 mg) supplementation, both of synthetic origin, significantly reduced acute adverse effects of radiation therapy to the larynx and overall at any site [11]. Two additional papers were published from the study, reporting the results of α-tocopherol supplementation only on recurrence rates of cancers [12] and mortality rates [13], the β-carotene supplementation having been discontinued after 156 patients had enrolled into the study because of

ethical concerns following the release of the Beta-Carotene and Retinol Efficacy Trial (CARET) results [89], another study discussed later in this chapter (as it has been criticised for being flawed).

The results did not look good—those patients taking the α-tocopherol supplements apparently had increased recurrence rates of cancers and a higher rate of second primary cancers compared with the placebo group [12] and lower survival rates [13]. However, re-analysis of the data indicated that the association between the supplementation and increased recurrence and lower mortality was only in smokers [165]. When they removed this confounding factor, there was no association between supplement use and decreased survival rates [165].

A study in mice found that Vitamin E may increase tumor progression and accelerate lung cancer [221], however this used the synthetic form of Vitamin E, aTOA. A prospective study found that in humans, there was a small, increased risk of lung cancer (HR 1.05 for every 100-mg/d increase in dose), and that the risk was largely confined to current smokers [233]. Again aTOA was the predominant form of Vitamin E taken in this study. The findings can't be extrapolated to other analogues or the non-synthetic versions of Vitamin E.

A promising analogue for cancer therapy

One of the analogues of α-tocopherol, dl-alpha tocopheryl succinate (aTOS), that has been extensively investigated shows promise as an anticancer agent alone and in conjunction with chemotherapy and radiation therapy [113]. This analogue does not have redox properties and therefore does not have antioxidant capacity. It has been found to be able to protect normal cells from chromosomal damage and at the same time potentiate cytotoxicity of chemotherapy and radiation therapy in cancer cells [113, 196]. Some of the research findings are as follows:

- aTOS has been found to be able to potentiate the apoptotic effects of doxorubicin [283] and enhance the cytotoxic effects of adriamycin on prostate cells [211].
- In vitro research has shown that lower than therapeutic doses of aTOS was able to synergize with the apoptotic effects of placlitaxel on non-small cell lung cancer [148] and increase the cytotoxic effects of paclitaxel on bladder cancer (both in vitro and in vivo) [114].
- In vitro research indicates it may also be able to decrease the genotoxic effects of bleomycin, protecting the white blood cells, in people with head and neck cancer [246].
- Rodent studies have demonstrated a reversal of the anti-gonadal effects of cyclophosphamide including lowered testosterone and disruption to sperm production [79].
- aTOS has been found to be able to enhance the growth-inhibitory effect of radiation, some chemotherapeutic agents, hyperthermia and biological response modifiers on tumor cells, and at the same time, protects normal cells [196].

Cell line studies have found that aTOS is able to inhibit cell proliferation and induce apoptosis in melanoma, breast, prostate, pancreatic, gastric colon,

lymphoma, glioma, neuroblastoma, leukemia, and oral squamous cell carcinoma [113], and can inhibit invasiveness of prostate cancer [281]. Importantly it does not affect the proliferation of most normal cells [196]. Animal studies have also demonstrated that this analogue can inhibit the growth of oral cancer [226], breast cancer [157], melanoma [158], and lung cancer [201].

Vitamin E and Vitamin C together

Vitamin C is needed to replenish Vitamin E activity; ascorbate reacts with the tocopheroxyl radical that arises due to Vitamin E's antioxidant activity and regenerates tocopherol as well as transferring the oxidative challenge to the aqueous phase (Vitamin C is water soluble, Vitamin E is lipid soluble). The ascorbate radical is then reduced back to Ascorbic Acid [80].

Professor Sali prescribes these two vitamins together as supplements.

Recommended Dose:

- A supplement containing a combination of the tocopherols and tocotrienols is recommended. Dosage may vary however in general, 1 standard capsule twice daily.

Selenium

Selenium can be synergistic with Vitamin C and Vitamin E to maintain normal blood (no stickiness) but there is some evidence that on its own, it can be protective against cancer and may be beneficial in treatment. Selenium has been primarily considered to have antioxidant, anti-inflammatory and anti-viral activity, however there is emerging evidence of its role in several of the pathways involved in cancer including cell proliferation, migration, invasion and angiogenesis [41].

Selenium is an essential micronutrient and is co-translationally incorporated into polypeptides in the form of selenocysteine, the 21st amino acid. It functions as a redox gatekeeper via incorporation into proteins that decrease intracellular oxidative stress. There are three categories of selenoproteins, and the effects of selenium are specific to particular forms of selenium [41].

There is some evidence from human studies that selenium may be protective against cancer, though not all studies have found a positive result. A recent large prospective cohort study found that hepatocellular carcinoma (HCC) and gallbladder and biliary tract cancers (GBTC) were significantly associated with lower circulating selenium and selenoprotein P concentrations, and that higher levels of both of these were significantly associated with reduced risk of HCC [101]. Some other key studies are set out in Table 7.2.

There has been much research into the potential role of selenium in the development of cancer and its effect on the cancer terrain. In vitro studies indicate that selenium compounds and selenoproteins can inhibit cell proliferation, motility, migration, and invasion, and reduce angiogenic factors in some cancer cells. Animal studies have also demonstrated that selenium can reduce micro-vessel

Table 7.2 Studies of selenium in humans

• Meta-analysis found that epidemiological data demonstrated reduced cancer incidence and mortality with higher selenium exposure [59]
• The Health Professionals Follow-Up Study demonstrated a strong inverse association between pre-diagnostic selenium levels and risk of advanced prostate cancer, suggesting that higher levels may slow prostate cancer tumor progression [141]
• The Nutritional Prevention of Cancer Trial, a randomised controlled trial (RCT) of 1312 subjects, found that selenium supplements (200 μg/day) was not associated with reduced recurrence of squamous cell carcinoma and basal cell carcinoma (the primary outcome variables), however it did find that it was associated with a reduction in secondary variables: incidence of prostate (63% reduction), plus reductions in incidence of total cancer (39% reduction, HR 0.61), colorectal, lung and overall cancer mortality in male participants during 1983–1993 [45]. An analysis of the data through to 1996 indicated that selenium's protective effect was confined to males, and that only a reduction in incidence of total cancer and prostate cancer was statistically significant, with those men with lowest baseline levels benefiting the most [67]
• The Selenium and Vitamin E Cancer Prevention Trial (SELECT), an RCT, failed to demonstrate a preventive effect of selenium supplementation on incidence of prostate cancer [149]
• Studies in China demonstrated a protective effect of selenium supplementation against liver cancer [277] and stomach cancer [23] though the studies have been criticised for unclear methodology [33]
• A meta-analysis found that there was a gradual reduction of risk of prostate cancer with level of plasma selenium at concentrations of 135–170 ng/mL (reduction of risk of 15% and 25% respectively) compared with those with lower levels (60 ng/mL) and that the risk of advanced prostate cancer was reduced by 40% and 50% at 135 and 170 ng/mL respectively [103]. The greater effect on advanced disease compared with the effect on localised tumors suggests that selenium interferes with prostate cancer metastasis [41]
• A Cochrane Review found that in four RCTs selenium may have a beneficial effect on the incidence of gastrointestinal cancer, however three had poor methodology [18]
• A Cochrane Review found limited evidence that people with higher levels of selenium had a lower cancer incidence though cautioned that this may be due to other confounding lifestyle factors and did not constitute evidence of an association between selenium and cancer incidence [254]
• Higher levels of circulating selenium and selenoprotein P were both significantly associated with reduced risk of hepatocellular carcinoma (HCC) but not with gallbladder and biliary tract cancer (GBTC) or intrahepatic bile duct cancer (IHBC). The Odds Ratio per 20 μg/L increase in circulating selenium concentration was 0.41, that is a reduction of 59% in risk per 20 μg/L increase in circulating selenium. The Odds Ratio per 1.5-mg/L increase in selenoprotein P concentration was 0.37 [101]

density and metastasis in a number of different cancers [41]. However, the inhibitory effect of selenium on metastasis may be specific to only certain forms of selenium; more research is needed to elucidate why this is the case [41].

Taken as a whole, there is a growing body of evidence that selenium may be protective against cancer as well as having anti-cancer including anti-metastatic properties.

Researchers have found that it is the basal plasma selenium levels that are critical to its preventative effect [41, 45, 205]. There is some evidence from studies that

supplementation in people who already have an adequate intake of selenium may increase the risk of type-2 diabetes: in the SELECT study, this risk was non-significant (7% increase) [149], however in another study the risk was significantly increased in the group with the highest levels of selenium [237]. There was also a non-significant risk of increased total cancer incidence found in the Nutritional Prevention of Cancer Trial in those in the highest selenium group [67]. The statistical non-significance means this may have occurred by chance.

Animal research indicates a U-shaped association between selenium status and anti-cancer effects including damage to prostatic DNA [263] and apoptosis in prostatic epithelial cells (with the highest apoptosis occurring where selenium levels were mid-range) [43]. The benefits of additional selenium may be due to upregulation of apoptosis rather than an anti-oxidant effect [43], however more research is needed.

The implication of a U-shaped dose-response curve is that those with low selenium are likely to benefit from selenium, but those with adequate-high levels may be adversely affected [205]. Thus selenium levels should be checked prior to supplementation.

Recommended Dose (in those who have low selenium levels):

- 100–200 μg/day (depending on nutritional status) (2–4 tablets daily of 50 micrograms each)

Natural Selenium Source = Brazil Nuts Note that brazil nuts are a good source of selenium. A study has found that just two brazil nuts a day was as effective as 100 micrograms of selenmethionine per day, over 12 weeks, in increasing selenium status and enhancing glutathione peroxidase activity (this is a selenium-containing enzyme with important antioxidant capacity), and only one brazil nut per day was sufficient to increase selenium level to within recommended intake levels of selenium [244].

Fish Oils

The benefits of fish oils as major sources of Omega 3 fatty acids (n-3 polyunsaturated fatty acids) was discussed in Chap. 3 Nutrition. Fish oils have been found to antagonize cancer cells and increase immunity. Fish oils are known to be cardio-protective in patients with and without diagnosed coronary heart disease, can decrease triglycerides, and improve mood. Fish oils have anticoagulant properties and thus can help reduce blood stickiness which often occurs in cancer. Fish oils have been found to competitively inhibit cyclo-oxygenase (COX), decreasing the synthesis of thromboxane A_2 from arachidonic acid in platelets (which normally plays an important role in coagulation). Fish oils may also decrease platelet growth and clotting factors [243].

Whilst there have been safety concerns about the potential for fish oils to cause increased bleeding in patients taking blood thinning medication, this remains a theoretical possibility that is not reflected in human studies [243]. The Australian Therapeutic Goods Administration reports that '*regulatory agencies consider that fish oil and omega-3 fatty acid containing products are safe with some requiring warnings about the theoretical possibility of bleeding events and drug interactions in their product information*' [243].

Blood stickiness should be assessed using Live Blood Analysis before and three months after supplementation and dosage adjusted accordingly. Fish oil should be from a high quality wild Alaskan salmon rather than farmed salmon or salmon imported from fish farms.

Where doses of <2 g daily of the omega-3 fatty acids in fish oil, eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) are taken, serious side effects are rare. Side effects can include heartburn, nausea, loose stools and rash. People with a known allergy or hypersensitivity to fish or other fish products, including shellfish, should not take fish oil supplements [243].

Recommended Dose:

- 1.8 g twice daily (EPA 720 mg, DHA 480 mg)
- During chemotherapy take 2 x 1.8 g twice daily

If a person is eating a lot of fatty fish, for example, salmon, the dosage may be adjusted accordingly.

Probiotic Supplements

Immunity cannot function normally when the gut doesn't have normal microbes. As discussed in Chap. 2 on stress, the gut microbiome plays an essential role in the functioning of the body and there is evidence of a role in cancer. Whilst we don't yet know everything there is about the gut microbiome, there is increasing scientific research and we do know we need our gut microbiome to be functioning well. If the gut microbiome is destroyed with chemotherapy or antibiotics, immunity is disturbed. Underactivity of the immune system can leave people vulnerable to increased infection and can lead to cancer years later. Overactivity of the immune system can lead to allergies and over longer periods, autoimmune diseases.

If the patient hasn't been eating fermented foods (e.g. kimchi, sauerkraut, kombucha tea, kefir, or yoghurt) then a probiotic tablet is recommended. The best ones tend to be those that require refrigeration. Non-refrigerated ones have a longer shelf life however they are not as well researched as the refrigerated ones in general.

It is important to feed the microbes with pre-biotics. See Chap. 3 Nutrition for more information.

Recommended Dose:

- A probiotic tablet containing 25–50 billion microbes per capsule taken last thing at night, as there is less stomach acid at this time (at other times, the stomach acid may destroy the probiotics).
- Patients on chemotherapy: use a higher dose probiotic during chemotherapy: 50–100 billion microbes per capsule.

Patients need to feed the microbes with pre-biotic foods.

Additional Dietary Supplements

Supplements are costly and so it is important to be sensitive to the patient's financial capacities when prescribing supplements, as creating financial pressure may add to existing stress.

Table 7.3 sets out additional supplements (in alphabetical order) that may also assist, and can be added to the basic supplements if finances allow. In terms of dosages, in general Professor Sali recommends taking twice the recommended dosages listed on the bottle for patients with cancer. Some general recommendations of dosages are set out below.

Table 7.3 Additional supplement list

Supplement	Recommended dose (also see notes on individual supplements)
Chlorella	May be taken as a powder or capsule. For a capsule with 96.2% organic chlorella powder, 3 capsules twice daily
Cinnamon Supplement	For a tablet with 1 g cinnamon, take 1–2 tablets twice daily
Co-Enzyme Q10	150 mg 1–2 times daily
Curcumin Supplement	500–4000 mg daily
Ginger Root	For treatment of nausea: 500 mg once or twice every 4 h For general anti-inflammatory purposes, 500 mg tablet once or twice daily (dosages depend on purity of ginger)
Green Tea (*Camellia sinensis*) tablets	Dosage depends on quality of the green tea. For a tablet containing the equivalent to 24.3 g of dry leaf, 1 tablet per day
Levo-Carnitine (L-carnitine)	For 500 mg tablets, 2 tablets twice daily Small body weight person: 1 tablet twice daily
Hi Maize	20–30 g per day
PSK (containing lentinan from mushrooms)	3 g PSK per day
Saw Palmetto	For a tablet containing 2 g of dry fruit, 1 tablet twice daily
St. Mary's Thistle	For a tablet containing 2.5 g silybum (equivalent to flavonol lignans calculated as silybin 28.6 mg), 1 tablet twice daily
Whey Powder	20–30 g per day

Chlorella Supplements

Chlorella is a blue-green algae native to Taiwan and Japan which is rich in phytonutrients including chlorophyll, amino acids, beta-carotene, potassium, B-complex vitamins, phosphorus, biotin and magnesium. There are several health benefits of Chlorella including:

- Detoxifying heavy metals
- Boosting the immune system and protecting against adverse effects of chemotherapy and radiation therapy
- Supporting the immune system and assisting NK cell activity and T Cell activity
- Lowering cholesterol and blood sugar and improving insulin sensitivity of cells [72, 171].

There are several species of the alga Chlorella, including both marine species (e.g. *C. ellipsoidea*, *C. salina*, *C. luteoviridis*, and *C.stigmatohora*) and freshwater species (e.g. *C. vulgaris*). *C. vulgaris* has been found to have strong antioxidant capacity in free radical scavenging, ferric reducing ability and metal chelating capacity.

Chlorella manufactures its own glutathione to protect itself from oxidation that occurs as part of photosynthesis. Higher doses of Chlorella have been found to have a stronger antioxidant capacity in limiting lipid peroxidation compared with lower doses and compared with synthetic glutathione [15].

Chlorella may be a useful adjunct by reducing toxicity in the body, in particular where cancer may have been initiated due to exposure to toxic substances (e.g. pesticides on farms). The polysaccharides produced in the cell walls of the Chlorella species are responsible for its chelating effect, though research indicates that not all polysaccharides excreted by the cell walls of algae have metal-chelating activity [116].

Some of the research evidence of its beneficial effects are set out in Table 7.4.

Recommended Dose:

- May be taken as a powder or capsule. For a capsule with 96.2% organic Chlorella powder, 3 capsules twice daily

Cinnamon Supplements

Cinnamon has been shown to lower insulin by increasing insulin sensitivity, and it also decreases angiogenesis associated with proliferation of cancer cells. Cinnamon has been shown, in in-vitro, animal and human studies, to improve all of the variables associated with Metabolic Syndrome: insulin resistance, increased blood glucose and lipid levels, decreased anti-oxidant activity, increased glycation of

Table 7.4 Research into the beneficial effects of Chlorella

Effect	Research
Beneficial actions in a range of cancers	Lung: Extracts were found to inhibit several human lung cancer cell lines is a dose-dependent manner, and reduce the migration of tumor cells [259] Liver: Animal studies have demonstrated that *C. vulgaris* can induce apoptosis in liver cancer induced in rats [9] Colon: Both *C. vulgaris* and *C. ellipsoidea* contain carotenoids, and extracts of these species of Chlorella have been found to inhibit human colon cancer cells in a dose-dependent manner. Whilst both were able to induce apoptosis, *C. ellipsoidea* extract's ability to do so was 2.5 times stronger, suggesting that the bioactive carotenoids (xanthophylls) in *C. ellipsoidea* show promise as a cancer-preventing compounds [37]
Anti-metastatic ability	A glycoprotein extract of *C. vulgaris* was found to induce T cell activation in peripheral lymph nodes in tumor-bearing mice, thereby augmenting anti-metastatic immunity through activating T cells and enhancing recruitment of these cells to tumor sites [240]
Stimulates the immune system	A randomised controlled trial of eight weeks' supplementation with Chlorella found a beneficial immune-stimulatory effect in healthy adults, including enhanced NK cell activity and produced interferon-γ, interleukin-12 and interleukin-1β, the T helper 1 cell-induced cytokines [129]
Protects against radiation damage	*Chlorella vulgaris* E25 (containing Beta-Carotene and Chlorophyll and other constituents) was found to exert a radioprotective effect in whole-body irradiated mice. The frequency of micronucleated polychromatic erythrocytes (MnPCEs) in bone marrow cells in mice was reduced by 25–40% when it was given not earlier than 1 h before (acute of chronic pre-treatment) or 15 min after irradiation. E25 was found to only be protective at dosage of 400 mg/kg body weight and the radioprotective effect disappeared at very high doses (3 × 500 mg/kg body weight per day) with a concurrent weight loss occurring, indicating what is probably the upper limit of tolerance for mice [219] Oral administration of mutant *C.vulgaris* E-25 in mice exposed to sublethal gamma rays increased the number of endogenous spleen colony forming units (E-CFU). The radioprotective effect was dependent on the dose and time of administration, with an optimal result found with 500 mg/kg body weight 1 h before or immediately after irradiation. There was a significant recovery in number of bone marrow cells and spleen weight also [229]

(continued)

Table 7.4 (continued)

Effect	Research
Accelerates recovery from chemotherapeutic agents	*C. vulgaris* was found to accelerate the recovery from 5FU-induced myelosuppression and prolonged the survival of the tumor-bearing mice without affecting the anti-tumor activity of 5FU, and in addition, exerted an antitumor effect. These results suggest its potential for alleviating side effects of chemotherapy without affecting the anti-cancer effect of the chemotherapeutic agent [126]
Reduces toxicity in body	Animal experiments have demonstrated that *C. vulgaris* has immunomodulatory effects and be able to chelate heavy metals such as lead in the blood [200]

proteins and increased weight gain [199]. It has anti-inflammatory activities and has been found to alleviate factors associated with Alzheimer's and assist in ischaemic stroke (by blocking cell swelling) [199].

The anti-cancer effects of cinnamon include modulation of angiogenesis and the effector function of CD8+T cells. In a mouse melanoma model, cinnamon was shown to increase cancer cell apoptosis via inhibition of NFκB and AP1 activities [130]. Cinnamon extract has been found to be able to inhibit VEGF-induced endothelial cell proliferation and migration in vitro and tumor-induced angiogenesis in vivo [154]. Cinnamon polyphenol extract (CPE) may also be able to regulate anti- and pro-inflammatory and glucose transporter families (GLUT) gene expression [30].

Recommended Dose:

- For a tablet with 1 g cinnamon, take 1–2 tablets twice daily

Co-enzyme Q10

Co-enzyme Q10 (CoQ10) is a powerful intracellular antioxidant, and an important factor in mitochondrial respiration, being part of the essential electron transfer chain [50, 58]. CoQ10 can lower blood pressure [136], protect the heart from chemotherapy toxicity [50] and is likely to help improve brain health in addition to heart health. Preclinical and clinical studies suggest that CoQ10 administration during cancer therapy with drugs such as doxorubicin and daunorubicin can prevent anthracycline-induced cardio-toxicity. Importantly CoQ10 does not interfere with the anti-cancer action of the drugs and may even enhance their effects. The heart is particularly vulnerable to toxicity from these drugs as the mitochondria of cardiac cells differs from other cells of the body, possessing a unique enzyme on the inner mitochondrial membrane that reduces anthracylcines to semiquinones. This leads to severe oxidative stress and irreversible damage to mitochondrial DNA, which then leads to cardiomyocyte death (via apoptosis or necrosis). CoQ10 appears to prevent this

mitochondrial damage and therefore is protective against anthracycline-induced cardiomyopathy [50].

One could postulate that given CoQ10's vital role in mitochondrial function, if the Metabolic Theory of Cancer discussed earlier in Chap. 3 is in fact accurate (research shows that mitochondria are damaged and less in number in cancer cells), then this would be an important supplement to include. CoQ10 is depleted by cholesterol-lowering statin drugs [58], which can also deplete the anti-oxidant activity of Vitamin E [250].

Recommended Dose:

- 150 mg 1–2 times daily

Curcumin

Curcumin, a component of the well-known Asian spice turmeric (*Curcuma longa*), has been found to have anti-inflammatory, antiseptic, analgesic, antioxidant and anti-proliferative activity [203, 267]. Epidemiological studies suggest that the low incidence of colon cancer in India may be associated with the use of curcumin used in cooking [173]. Curcumin has a variety of anti-cancer actions via its effect on several pathways involved in cell cycle regulation, apoptosis, mutagenesis, oncogene expression, tumorigenesis, and metastasis [267].

Cell line research has elucidated some of the many pathways by which curcumin has an effect. For example, curcumin has been shown to inhibit lung cell proliferation [145], inhibit prostate cancer cell growth via inhibition of androgen receptor pathways [285], inhibit prostate cancer bone metastasis [64], and inhibit mesenchymal transition and invasion induced by cancer-associated fibroblasts (cancer-associated fibroblasts are key determinants of malignant progression of cancer, promoting tumor growth and angiogenesis) in prostate cells [65].

Curcumin is able to modulate many molecular targets including transcription factors, growth factors and their receptors, cell adhesion molecules, enzymes, cytokines and genes (that regulate cell proliferation and apoptosis) that are involved in tumor growth, angiogenesis and metastasis [1, 65]. Curcumin can modulate the growth of tumor cells through several cell signalling pathways including cell proliferation pathways, cell survival pathways, caspase pathways, tumor suppressor pathways (p53, p21), death receptor pathways, protein kinase pathways and mitochondrial pathways [203]. Animal studies also indicate it is able to inhibit tumor initiation and tumor promotion [96, 203].

There is evidence that curcumin may be useful in the treatment of depression and anxiety. Given that these conditions can often occur in patients with cancer, this may be a useful additional supplement. A patented curcumin extract (BCM-95®) at low dose (250 mg twice daily) over 12 weeks has also been shown to be effective in treating depression and anxiety in a randomised controlled trial, with no additional benefit of doubling the dosage (500 mg twice daily) or adding saffron [153].

Another RCT of 500 mg curcumin (88% total curcuminoids) over eight weeks found that it was significantly more effective than placebo in alleviating several mood-related symptoms, and greater efficacy was found in a subgroup of individuals with atypical depression [152]. Other studies have also found similar positive effects [217].

The combination of curcumin with the active constituents of other plants shows some promise and may enhance the bioavailability. For example, a combination of curcumin, arctigenin (an anti-inflammatory lignan from the seeds of *Arctium lappa)* and epigallocatechin gallate (EGCG, green tea polyphenol) had stronger anticancer effects than the single anti-cancer agents alone in breast and prostate cell lines [260].

Cancer stem cells (CSCs) make up only 0.2–1% of cancer cells, but these cells have the capacity to self-renew, continuously differentiate, are resistant to chemotherapeutic agents and play a critical role in cancer recurrence [204]. CSCs have been identified in breast, ovarian, head and neck, pancreatic and colon cancer, and research has demonstrated that there are particular signalling pathways that can regulate growth of CSCs [204]. Curcumin and piperine, alone and in combination, have been found to inhibit breast stem cell self-renewal but do not cause toxicity to differentiated (normal) cells. Both curcumin and piperine were found to inhibit Wnt signalling, one of the pathways regulating CSC growth [115].

Curcumin is radio-protective and radio-sensitizing, protecting normal cells against the deleterious effects of radiation therapy whilst enhancing the effect of radiation. It is thought that its radio-protective effect may be due to its ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammation. Its radio-sensitizing effect may be due to upregulation of genes responsible for cell death [109].

Curcumin has also been found to sensitize silymarin (the bioactive component of St. Mary's Thistle) to exert synergistic anticancer activity in colon cancer cells: the combination was able to inhibit colon cell proliferation and increase apoptosis compared to when the cells were treated with the single compounds [175].

Unfortunately, curcumin is poorly absorbed and so it is often combined with other substances such as ginger to increase its absorption. There are commercially available tablets containing ginger and turmeric. The best supplements contain curcumin at $\geq$ 75% concentration (typical doses range from 500 to 4000 mg daily [5].

Recommended Dose:

- 500–4000 mg daily

Ginger Root

Ginger (Zingiber officinale Rosc) has antioxidant and anticarcinogenic properties [208]. Several of its active constituents show promise as anti-cancer compounds. For example, an active, pungent constituent of ginger, 6-shogaol, produced when the root is dried or cooked, has been found to destroy breast CSCs through a variety of

mechanisms [204]. These mechanisms include inducing mitotic arrest and viability of gastric cancer cells, inducing aberrant mitosis followed by apoptosis in colon cancer cells, inducing oxidative stress leading to apoptosis in hepatoma cells, inducing autophagy in HNSCLC cells and inhibiting invasion in breast cancer cells [204].

Recently an in vitro study found that 6-shogaol shows anti-proliferative activity against breast cancer cells and spheroids (these are 3-Dimensional cultures of cells modelling stem cell-like cancer) and was able to suppress the size and colony-forming ability of spheroids. The study found that 6-shogaol was able to significantly affect the cell cycle, resulting in cancer cell death, reduce the expression of CD44/CD24 CSC surface markers in spheroids, induce programmed cell death primarily via autophagy induction (apoptosis was a secondary inducer), suppress the size and colony forming ability of spheroids by altering the Notch signalling pathway (Notch signaling has been found to be actively involved in stem cell self-renewal), and directly kill cancer cells via a cytotoxic effect. These cancer-destroying effects occurred at concentrations that were not toxic to normal cells. In comparison to the drug Taxol used as a control, for two types of breast cell lines 6-shagaol was effective in both cell lines and spheroids, but Taxol (which showed an inhibitory activity in monolayer cells) did not show inhibitory activity against the spheroids even at 10,000-fold higher concentration compared with 6-shogaol. The concentrations of 6-shogaol required to inhibit spheroids was found to be safe to non-cancerous cells [204].

Other research has demonstrated that another of the active constituents of ginger, [6]-gingerol, exerts anti-inflammatory effects through modulation of NF-kappaB (NF-kB). NF-kB is activated in epithelial ovarian cancer cells and may contributed to increased angiogenesis. Ginger was found to inhibit the growth of ovarian cancer cell lines (6-shogaol was found to have the strongest effect when individual constituents were examined) and was able to inhibit NF-kB activation and decrease secretion of angiogenic factors, VEGF and interleukin-8 (IL-8) [208]. Animal research has found that whole ginger extract exerts significant growth inhibitory effects and is cytotoxic to prostate cancer cells whilst having no adverse effect on normal prostate cells. Whole ginger extract shrunk prostate tumors by 56% in mice but did not demonstrate toxicity in normal, rapidly dividing tissue such as gut and bone marrows [119].

There is some evidence that ginger may also reduce platelet aggregation according to a systematic review, with four of eight clinical studies showing positive results and four showing no effect, and two observational studies demonstrating mixed results. The authors concluded that further studies were required [162]. As previously stated, people with cancer can have sticky blood.

In Chinese medicine, ginger is often used in Chinese herbal medicine prescriptions for its anti-nausea effect.

Recommended Dose of Ginger Root Supplements:

- For treatment of nausea: 500 mg once or twice every 4 h
- For general anti-inflammatory purposes, 500 mg tablet once or twice daily (dosages depend on purity of ginger)

Green Tea Supplements

Taking a green tea tablet is a handy way of getting the benefits of green tea, in particular if the taste of green tea isn't to the patient's liking. Green tea tablets from a reputable company may contain as much as the equivalent of 11.6 cups of green tea per tablet (and an amount of caffeine equivalent to what you would get in two cups of tea, therefore low caffeine), and are a convenient way of getting the benefits of green tea. As discussed in Chap. 3 Nutrition, green tea contains several active constituents that have a range of actions on cancer pathways.

Recommended Dose:

- Dosage depends on quality of the green tea. For a tablet containing the equivalent to 24.3 g of *Camellia sinensis* dry leaf, 1 tablet per day

Hi-Maize

Hi-Maize is a corn derivative and a source of resistant starch. Research indicates that there is a direct link between diet, colonic bacteria and colon cancer, and animal studies have found that diets high in resistant starch may prevent colon cancer [209].

Recommended Dose:

- 20–30 g per day in juice, in soup, on top of breakfast cereal or as part of a healthy smoothie (drink)

Levocarnitine (L-carnitine)

Levocarnitine (L-carnitine) is synthesised within the body and may also be obtained via diet. It is involved in the transportation of fatty acids into mitochondria and the maintenance of homeostasis in key mitochondrial lipids and proteins. There is some evidence that L-carnitine may protect neural tissue from chemotherapy-induced toxicity [207]. Low serum levels of L-carnitine have been found in cancer patients with cachexia, and is implicated in its pathogenesis [227]. Some studies have found L-carnitine to be useful in improving energy and quality of life in those with cachexia [227] and cancer-related fatigue (CRF) [55] as well as non-anaemic fatigue following chemotherapy [82]. L-carnitine may also improve erectile dysfunction following prostatectomy [207]. However, it has not been found to be beneficial in decreasing CRF in advanced cancer patients [56, 207]. Supplementation is safe with only minor adverse events [207].

Recommended Dose:

- For 500 mg tablets: 2 tablets twice daily
- For small body weight person: 1 tablet twice daily

Mushroom Extract Supplements

As discussed in Chap. 3 Nutrition, there are several kinds of mushrooms including Ganoderma lucidum (*Ganoderma lucidum*, Chinese herb Ling Zhi) which have been shown to have anti-cancer properties. There are several mushroom extract tablets on the market, and some combine different types of mushrooms. Mushroom proteins contain all the essential acids and are particularly rich in lysine and leucine [257].

The main active constituents in *G. lucidum* are polysaccharides, peptidoglycans, and triterpenes [257]. The polysaccharide component has a variety of effects on the body including: anti-inflammatory, hypoglycemic, antiulcer, antitumorigenic, and immunostimulating effects [257]. It also contains proteins and lectins which may contribute to its medicinal properties [257]. In vitro research has demonstrated that it can induce cell-cycle arrest and apoptosis in many different types of human tumor cells, as well as inhibiting cell adhesion, invasion and migration and angiogenic factors [257]. In animal studies, a triterpene rich extract pf *G. lucidum* has been found to suppress prostate growth induced by testosterone [150], and an active constituent isolated from it, Ganoderol B was found to bind to the androgen receptor and inhibit 5α-reductase, suppress androgen-induced LNCaP cell growth, and down regulate Prostate-Specific Antigen (PSA) [151]. In human studies of patients with advanced stage cancers, supplementation with *G. lucidum* capsules (1800 mg/day for 12 weeks) resulted in significant enhancement of cellular immunity (elevated IL2, IL6 and interferon γ in 80% of patients [75].

In another study, this time in lung cancer patients, total T Cells, NK cells and CD4/CD8 ratio was significantly improved in the group treated with *G. lucidum* supplements and in 65% of patients, quality of life (Karnofsky score) was improved also [76]. There is substantial evidence that *G. lucidum* acts as an immune-stimulator, and it can act as an anti-oxidant as well as having a hypoglycaemic effect and being hepato-protective [257].

Polysaccharide K (PSK) contains the active ingredient lentinan from various fungi including coriolus versicola and shitake mushroom. A randomised controlled trial (RCT) found that oral protein-bound polysaccharide K (PSK) plus tegafur/uracil significantly increased the five-year disease-free survival compared with tegafur/uracil alone (73% versus 59%) in patients with stage II or III colon

cancer. PSK plus tegafur/uracil also significantly reduced the recurrence of colon cancer by 43.6% and mortality by 40.2% and prevented the recurrence of lung metastases [191].

Recommended Dose:

- 3 g PSK daily

Saw Palmetto Supplements

Saw palmetto (*Serenoa repens*) is a herb that has been used to treat benign hyperplasia of the prostate. Whilst some observational studies have failed to find an association between saw palmetto supplementation and risk of prostate cancer [25], in vitro research suggests that the herb may have anti-cancer properties. These include being able to arrest growth of prostate cells, induce apoptosis, decrease Prostate Specific Antigen (PSA) levels and disrupt the AR signal pathway and inactivate STAT3 signalling in prostate cancer cells [276]. Saw palmetto is usually combined with other nutrients that are useful in treating prostate problems including, for example lycopene, selenium, zinc, curcumin, stinging nettle (*Urtica dioica* root), and reishi mushroom.

Recommended Dose:

- For a tablet containing 2 g of dry fruit, 1 tablet twice daily.

St. Mary's Thistle (Milk Thistle)

The fruit and seeds of the milk thistle *Silybum marianum* (L.) Gaertn, also known as St. Mary's Thistle, have been used for more than 2000 years to treat liver and biliary disorders. Traditionally the leaves have been used in salads, the fruits roasted to form a coffee substitute, and the seed-like fruits used for medicinal purposes. Its active constituent is silymarin which primarily consists of falonolignan isomers Silybin A and Silybin B, isosilybin A and isosilybin B, silychristin, silydianin, and their flavonoid precursor, taxifolin. Silybin A and B are collectively often referred to as silibinin. Most supplements are standardized according to their silibinin content. Milk thistle is usually produced as an extract in capsules or tablets rather than as an herbal tea as the active constituents are lipophilic [181].

Much of the research into this plant has focused on its effect on the liver. Silymarin has been found to stabilize cell membranes, stimulate detoxification pathways, and stimulate regeneration of liver tissue. It is also showing promise as a potential therapeutic agent in cancer [181]. Research has demonstrated that silymarin can inhibit growth of certain cell lines including prostate cancer [286] and have a

cytotoxic effect on prostate, breast and ectocervical tumor cells [17]. Silymarin was found to exert a dose-dependent inhibitory effect on drug-resistant ovarian cancer cells and doxorubicin-resistant breast cancer cells and may increase the efficacy of cisplatin and doxorubicin against ovarian and breast cancer cells [223]. Research in cell lines indicates that it does not stimulate growth of leukaemia cells [68].

Research shows that silibilin shows promise in prevention and treatment of liver cancer. It was found that silibilin can significantly decrease the growth of human liver cancer cells, via reducing cancer cell proliferation and cell cycle progression, enhancing apoptosis, and altering the chromatin structure of cancer cells [131]. As mentioned previously, the combination of curcumin and silymarin work synergistically to increase colon cancer cell apoptosis and inhibit colon cancer cell proliferation [175].

Recommended Dose:

- For a tablet containing 2.5 g silybum (equivalent to flavonol lignans calculated as silybin 28.6 mg), 1 tablet twice daily

Whey Powder

Whey powder may be a useful source of proteins, and may assist cancer patients to maintain muscle mass during treatment, in particular when appetite may be poor, and may decrease the side effects of cancer treatments [120].

Recommended Dose:

- 20–30 g per day in juice or in soup or on top of breakfast cereal or as part of a healthy smoothie.

Intravenous High Dose Vitamin Therapy

The advantage of intravenous (IV) injections of Vitamin C and other supplements is that the dosage can be much higher than consumed in a tablet form, and it goes straight into the bloodstream, bypassing the gut. There are several vitamins that may be administered intravenously including Vitamin C, Vitamin B12, B Complexes [61], trace elements, Glutathione, and α-Lipoic Acid. Some Chinese herbal medicines are commonly administered intravenously within Chinese hospitals where Chinese herbal medicine (and acupuncture) are routinely integrated with orthodox western medical treatment of cancer.

High Dose IV Vitamin C

The anti-cancer mechanisms of high doses of ascorbic acid (ascorbate) include but are not limited to, cytotoxicity to a number of cell lines (mostly malignant) via pro-oxidant activity, inhibiting cell proliferation via inhibiting prostaglandins (2 series), and inhibition of angiogenesis [80, 81]. High doses of ascorbate may also increase ATP production [81]. Ascorbate and its radical potentiate the activation of NF-κB which is associated with inhibition of cell growth, and it can generate hydrogen peroxide (enhanced by iron and copper) which may generate further ROS which can damage the cell membranes of malignant cells (in contrast, in healthy organisms, these oxidative reactions only form in minute quantities) [80].

Ascorbate may also protect against nitrate-induced carcinogenesis and in large quantities, enhances removal of sodium in the urine (sodium/potassium ratio is disturbed in cancer) and may also inhibit prostaglandins (of the 2 series) in cancer cells [80]. The collagen-rich extracellular matrix provides a barrier to the metastasis and invasion of cancer cells, and lack of ascorbate leads to instability of the collagen structure which is commonly seen cancer [80]. In addition, Vitamin C may exert anti-tumorigenic actions by decreasing levels of hypoxia-inducible factor (HIF)-1 which is a transcription factor that targets VEGF and plays a role in angiogenesis [77]. Thus, the actions of Vitamin C appear to go beyond what was originally thought to be its primary mode of action, as an anti-oxidant.

Cell studies have demonstrated that cultured colorectal cancer (CRC) cells with KRAS or BRAF mutations (which occurs in more than 50% CRC) are selectively killed by high levels of Vitamin C due to increased uptake of dehydroascorbate (DHA, the oxidized form of Vitamin C) via the GLUT1 glucose transporter. Intracellular DHA is reduced to Vitamin C and depletes glutathione, with reactive oxidative species inactivating glyceraldehyde 3-phosphate dehydrogenase (GADPH), leading to cell death [280].

High dose IV ascorbic acid, but not oral ascorbic acid, has been shown to produce plasma concentrations that produce hydrogen peroxide in the extracellular space that results in cytotoxicity. This pro-oxidant activity was thought to be the main means by which it inhibits cancer growth and metastasis, and that its role as an energy intermediate may constitute a secondary mechanism [80]. However, this argument has been questioned by Dettman and Meakin [60] who argue that high dose Vitamin C is actually a reducing agent and not acting as a pro-oxidant, as it donates electrons, and rather, it is the oxidized form of Vitamin C, dehydroascorbate (its redox pair) that accepts electrons and is an oxidizing agent.

The mechanisms by which Vitamin C works in cancer are, as yet, unproven and largely unknown. Multiple mechanisms have been researched and H_2O_2 production is only one of them. H_2O_2 production experimentally depends on the media and techniques used. It is not clear at all that this happens in vivo. Ascorbate is a reducing agent—it donates electrons. That's it. It can't oxidise anything. H_2O_2 production is a theory that has propelled Vit C into clinical research, however clinical results in studies have not been anything like those seen in laboratory

studies. How Vitamin C works in cancer is a much deeper issue than the pro-oxidant theory in humans [61].

It is thought that the selective toxic effect is likely to be due to that fact that IV administration allows plasma levels of ascorbate to reach higher levels than when administered orally, and the higher levels can be sustained for longer periods of time [80]. Studies have confirmed that plasma Vitamin C concentrations vary with the route of administration and it is only with IV administration that the necessary Vitamin C levels needed to kill cancer cells are reached in plasma and urine. The efficacy of IV Vitamin C needs to be researched; efficacy cannot be extrapolated from oral doses of the vitamin. There is relatively little pharmacokinetic data on high doses of IV Vitamin C, in particular in those living with cancer [66].

For further information about Vitamin C, see the discussion by Dettman and Meakin [61] in the Additional Reading Section.

IV Vitamin C and Surgery

IV Vitamin C may be used prior to and following surgery to assist in the body's recovery. Blood levels of Vitamin C are decreased following uncomplicated surgery and are even further decreased in surgical intensive care unit patients. The decrease in blood vitamin C levels may be due to increased demand caused by increased oxidative stress [73]. Thus high dose IV Vitamin C may be useful prior to and after surgery.

IV Vitamin C with Chemotherapy and Radiation Therapy

High dose IV Vitamin C has been found to increase the efficacy of chemotherapy and radiation therapy as well as decrease the adverse effects [80]. A German study found that IV Vitamin C administration for at least four weeks in breast cancer (stages IIa–IIIb) survivors undergoing chemotherapy or radiation therapy had a significant reduction in side effects induced by the disease or the cancer treatment, in particular nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness and haemorrhagic diathesis in comparison to women without this adjunct treatment. There were no documented side effects of the IV Vitamin C [255]. Laboratory research indicates that high-dose ascorbate increases radiosensitivity of glioblastoma multiforme cells to a much greater extent that astrocytes, resulting in greater cell death than radiation alone [92]. This suggests some promise in this particular cancer which is known to be very resistant to chemotherapy and radiation therapy.

Vitamin C in high concentrations (but not low concentrations) has been shown to enhance the cytotoxicity of 5-FU in a dose-dependent manner in mouse lymphoma [178]. Other preclinical studies have found that combining high-dose Vitamin C with arsenic trioxide is more effective than chemotherapy alone in ovarian cancer cells [187], and ascorbic acid plus gemcitabine is more effective in inhibiting pancreatic tumors in mice than gemcitabine alone [69]. In vitro research indicates that ascorbic acid plus gemcitabine may be more effective than gemcitabine alone in their cytotoxic effects on malignant mesothelioma cells [161].

In relation to ascorbate (Vitamin C), there was a suggestion that increased intracellular concentrations could provide cancer cells with a metabolic advantage based on the finding that cancer cells were able to acquire and concentrate ascorbic acid. But Gonzalez and colleagues explain that Vitamin C readily enters cancer

cells (since ascorbic acid and glucose, the main fuel of cancer cells, have similar molecular structures) via facilitative glucose transporters (GLUTs) and not only acts as an antioxidant but in high concentrations, has pro-oxidant effects and is therefore cytotoxic to cancer cells [80].

However, the story is a little more complex it seems. Dettman and Meakin [60] argue that megadoses of IV Vitamin C (ascorbate) actually act as a reducing agent (i.e. donates electrons) and that it is the *oxidized* form of Vitamin C, dehydroascorbate (the redox pair) that accepts electrons and is an oxidizing agent. High doses of the *reduced* form of Vitamin C, ascorbate, appear to be involved with production of substantial amounts of hydrogen peroxide and therefore has a pro-oxidant effect against cancer cells [60]. In contrast, the oxidized form dehydroascorbate has been found to inhibit the cytotoxic action of anti-cancer drugs when added to myeloid and lymphoma cell lines. They explain that in general, when ascorbate and not dehydroascorbate is used at the same time as chemotherapeutic agents, it will increase the cytotoxic action of the drug, and that it is likely that there are many mechanisms by which high dose Vitamin C works including generalized immune stimulation, inhibition of angiogenesis, hyaluronise inhibition, and collagen growth (which contains the tumors) [60].

Toxicity of Vitamin C

Vitamin C is relatively non-toxic at high levels (10–100 times the oral RDA), though some minor side effects have been reported including gastrointestinal disturbances, acidosis, oxaluria, renal stones, glycosuria, renal tubular disease, sensitivity reactions, conditioned need, prothrombin and cholesterol disturbances, vitamin B12 destruction, fatigue, and sterility [80]. Of these, gastrointestinal effects are most prevalent side effects (including stomach cramps, diarrhoea and nausea), and these may be reduced or eliminated by taking the ascorbic acid as a buffered salt or immediately after meals [80]. Many of the toxic effects are rare and of minor clinical significance [80].

There is no evidence that ascorbate increases the risk of kidney stones as ascorbate makes urine acidic and stones form mostly under alkaline conditions (calcium oxalate). However, patients with glucose-6-phosphate deficiency may be at risk of developing haemolysis when given high doses of Vitamin C so patients need to be screened for this prior to undergoing Vitamin C therapy. Intake of inorganic selenium (Na selenite) should be avoided whilst on high dose Vitamin C also [80].

High Dose IV Vitamin B12

Vitamin B12 is involved in one-carbon metabolism and cell division. The association between Vitamin B12 and cancer is not well understood. High levels of Vit B12 have been found in patients with particular cancers including blood and solid tumors, and in people with high levels of Vit B12, there is a higher prevalence of particular cancers and a greater chance of being diagnosed with cancer [7].

Supplementation with folic acid and Vitamin B12 is used to reduce Pemetrexed therapy toxicity [241]. A study in patients with malignant pleural mesothelioma found that patients supplemented with folic acid and Vitamin B12 tolerated chemotherapy better with less toxicity and more cycles of treatment. In addition, survival was five months greater than in patients who did not receive supplementation [222].

High Dose IV Glutathione (GSH)

Glutathione (also known as GSH) is a substance found within the body and in particular fruits, vegetables and meats. It is a tripeptide of glutamate, cysteine and glycine and is a powerful antioxidant, scavenging ROS, and immune system stimulator. It plays a critical role in many cellular processes including cell signalling and antioxidant defences and the detoxification of ROS or reactive nitrogen species [176]. It is also involved in the cell cycle regulation. Adequate GSH is required for adequate immune system functioning overall, and in particular, activation and differentiation of T cells. Disruption to GSH has been implicated in the aetiology and progression of cancer. It also plays an important role in the brain, including as a neuromodulator, neurotransmitter, and anti-oxidant [176].

When GSH is depleted, there may be increased susceptibility to oxidative stress that is part of the pathogenesis of a range of diseases, including cancer [245]. Depletion leads to disruptions of a range of systems and functions including the immune system, oxidative and nitrosative stress pathways, energy production regulation, intracellular signalling, epigenetic regulation of gene expression and the functioning and survival of mitochondria, amongst others [176]. It can also lead to increased inflammation.

Extracellular GSH has been found to inhibit the growth of tumor cell lines [287] and tumors [118]. Extracellular GSH has also been found to be able to induce apoptosis in ovarian cancer cells, mediated by hydrogen peroxide production and DNA damage [193].

Elevated glutathione in tumor cells is a function of cancer biochemistry and is endogenous; it is independent of exogenous GSH intake [61]. Elevated GSH in tumor cells can protect these cells in bone marrow, breast, colon, larynx and lung cancers and protect the tumor cells against chemotherapy [14]. Many forms of chemotherapy seek to block or reduce intracellular GSH levels, and this can be achieved in vitro. However, people are more complex and if GSH is depleted with drugs, the depletion will be systemic and this is problematic as GSH is essential for controlling toxicity in the body. Exogenous GSH does not influence the aberrant production of intracellular GSH, therefore it will not contribute to the problem. In fact, exogenous GSH may aid the patient from the point of view of controlling toxicity in their body as well as improving quality of life and helping increase chance of survival [61].

GSH and chemotherapy

GSH (glutathione) in conjunction with chemotherapy is somewhat controversial. In some human clinical studies, GSH therapy has been found to be associated with decreased toxic side effects of various chemotherapy drugs without decreasing the effects of the drug. For example, intravenous GSH has been found to be neuro-protective against the side effects of cisplatin in advanced gastric cancer [34], oxaplatin-based chemotherapy in advanced colorectal cancer [35, 169] and cisplatin plus carboplatin in patients with advanced ovarian cancer [24].

Several animal and clinical studies have also demonstrated that administration of IV GSH prior to cisplatin administration can reduce its toxicity without decreasing the effectiveness of the drug [51]. A combination of IV GSH and cisplatin has also been found to improve quality of life as well as reduce toxicity in women with ovarian cancer [234]. In some cases, the effect of the drug is increased. Other human clinical trials have shown less benefit but consistently have not demonstrated a decreased response from chemotherapy drugs (see Dettman and Meakin [61] in the Additional Reading Section).

Concurrent use of GSH and Vitamin C

A preclinical study (in vitro and mice tumor xenograft experiments) that investigated the effects of Vitamin C and GSH concluded that at physiological levels achievable by oral supplementation, the combination of Vitamin C and GSH is able to remove and quench ROS, however at high dose levels (supra-physiological), GSH (which has an antioxidant capacity, clearing H_2O_2) can antagonise the pro-oxidant action of ascorbic acid (AA)—it interferes with the H_2O_2 production of ascorbic acid which is the main anti-neoplastic mechanism of ascorbic acid [39]. The authors concluded that: 'These data confirm the pro-oxidative anti-cancer mechanism of pharmacologic AA and suggest that AA and GSH administered together provide no additional benefit compared with AA alone. There is an antagonism between ascorbate and glutathione in treating cancer, and therefore IV AA and IV GSH should not be co-administered to cancer patients on the same day' [39].

However, this study has been criticised on a number of levels by Dettman and Meakin [60] who argue that the amounts of Vitamin C and glutathione used in this in vivo mouse experiment were distinctly well above the pharmacological range used in comparison to the in vitro studies—that the amount of glutathione given to the mice was excessive (equivalent to 48 g/60 kg human), and that their results (graphs) do not demonstrate what the authors were arguing (that glutathione totally stopped the effect of Vitamin C in vitro). Dettman and Meakin argue that GSH may be a free radical scavenger at low concentrations and that if infused at the same time as IV Vitamin C, it is more likely to end up in many sites within the body, not just concentrating at the site of the cancer. Thus, they argue, it is likely that these lower levels of GSH help protect the body from the underlying oxidative stress that occurs in people with cancer [60]. This highlights an important issue, that of making

clinical recommendations on the basis of animal and in vitro experiments. Where there are methodological flaws that might have led to inadequate conclusions, this makes such advice potentially more spurious. The interpretation of in vitro and animal experiments is not easy for practitioners.

Conclusions about GSH as an adjunct therapy

Adjunct GSH therapy in cancer treatment aims to support the total antioxidant capacity of the patient and in general to assist with quality of life and side effects associated with conventional cancer treatment. There are no human clinical studies to date that demonstrate that supplemental GSH adversely impacts on the effects of chemotherapeutic agents or adversely affects the prognosis of the cancer patient. In general, results from in vitro or animal trials cannot be extrapolated to clinical outcomes in humans. At this point in time, case studies and clinical trials of GHS as an adjunct therapy have not demonstrated detrimental effects [61].

For more information on GSH see the Additional Reading section of this chapter.

IV α-Lipoic Acid

α-Lipoic Acid (ALA) is a cofactor that plays a role in enzyme complexes that control metabolism, including the conversion of pyruvate to energy in mitochondria. It can scavenge free radicals and reduce oxidative stress in several diseases including cancer [16]. ALA works in a number of ways as an anti-cancer agent on the cancer terrain. It has been found that ALA can induce hyperacetylation of histones, proteins active in the proliferation of cancer cells. ALA has been found to induce apoptosis in cancer cells, but not in normal cells [252]. Cell culture research has demonstrated that the addition of high doses of ALA inhibits NFkB activation which is known to be involved in regulation of inflammatory-induced gene function [239]. It is able to stabilise nuclear factor (NK)kB [138], which once activated induces more than 200 genes that suppress cell apoptosis and induce cellular proliferation, invasion, metastasis, chemo-resistance, radiation resistance and inflammation [2]. It has also been shown to stimulate pro-oxidant driven apoptosis in human colon cancer cells [266] and increase the concentration of homocysteine in cancer cells leading to cytotoxicity [102].

ALA is able to assist the proliferation of normal human lymphocytes and retard the proliferation of leukemia T cell lines [192] and correct functional defects in peripheral blood mononuclear cells in advanced cancer patients [160]. Addition of ALA to cell cultures of patients with cancer significantly increased the response of their mononuclear cells, demonstrating a positive effect on immune cell functioning in advanced cancer patients [160].

The Controversy About (Dietary) Antioxidant Supplements and Chemotherapy

About 60% of cancer patients are estimated to take antioxidants during standard therapy without the knowledge of their oncologist [197]. There has been a misconception that low dose, dietary antioxidant supplements might reduce the effectiveness of chemotherapy and radiation by reducing the free radicals needed to kill the cancer cells [80, 89]. Since some chemotherapy drugs work by strongly promoting oxidation and oxidant-induced apoptosis (including the anthracyclines such as adriamycin and epirubicin, the alkylating agents including chlorambucil, cyclophosphamide, thiotepa and busulfan, and the platinum drugs such as cisplatin and carboplatin), it was believed by some that anti-oxidants (e.g. Vitamin C at low dose) would interfere with the action of these drugs [6, 83]. Because of this misperception, many oncologists advise patients to not take anti-oxidant supplements during chemotherapy and radiation therapy, as the aim of these therapies is to induce ROS and thereby kill the cancer cells.

According to Dr. Keith Block, what may have also added to the misconception around antioxidants are the results of two large studies, The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [ATBC] and the CARET [89]. The CARET study (which had nothing to do with chemotherapy) found an increase in lung cancer associated with β-carotene intake, however the study had several flaws including using a synthetic form of β-carotene (rather than a natural form). In addition, the study population had significant exposure to alcohol and tobacco use and therefore internal environments characterised by oxidative stress- under such circumstances, Block argues it is very conceivable that the labile β-carotene may have converted from a protective anti-oxidant to a pro-oxidant. Similarly, according to Block, because α-tocopherol was also given as a single nutrient and it is also labile, in a subject with considerable oxidative stress it is not surprising that this also showed an increase in risk [89]. The point made by Block is that there was much press around these studies, all of which had nothing to do with chemotherapy and all of which were methodologically flawed, and this is likely to have contributed to the misconception that antioxidants are harmful [89].

Another important point that Block makes is that synthetic forms of antioxidants are not the same as the natural forms [89]. Finally, Block makes the point that it is problematic to look at single nutrients (e.g. α-tocopherol alone) because single nutrients won't have an electron-cushioning effect or 'network antioxidant' effect. He explains that network antioxidant refers to the process where an antioxidant donates its electron to an unpaired free radical to stabilise what would otherwise become a pro-oxidant, and in donating its electron, it now carries an unpaired electron itself and becomes a weak oxidant. However, another antioxidant then passes an electron to this weak oxidant to stabilise it and so on. Thus, this network effect of several antioxidants working together is able to diminish the adverse effects of pro-oxidants [89].

Experiments in cell cultures

There have been studies in cell cultures that have indicated that low dose Vitamin C may stimulate the growth of some cancer cells (without affecting normal cells) [195]. However it is difficult to extrapolate the findings of cell studies to the much more complex and dynamic system that is the human body. In addition, any nutrient placed into a cell culture at normal physiological levels will aid cells to grow—cancer cells need and use nutrients too. But cancer cells are not normally exposed to the high levels seen with pharmacological doses and concentrations; higher levels have toxic effects on cancer cells, demonstrated repeatedly in cell culture studies [61].

Oxidative stress and effectiveness of chemotherapeutic agents

Whilst the mechanism of action of particular types of chemotherapy drugs is believed to be, at least in part, the creation of high levels of oxidative stress that promotes apoptosis and kills the cancer cells, it has been argued that the oxidative stress might actually decrease the overall effectiveness of the chemotherapeutic agent since oxidative stress slows down the process of cell replication and it is during cell replication that the chemotherapy kills the cancer cells [49]. The argument is that slower cell replication means lower efficacy in killing cancer cells [6]. By adding antioxidants at particular doses to decrease oxidative stress, chemotherapy may be more effective—this was demonstrated in the case of tamoxifam therapy and co-administration of CoQ10, riboflavin and niacin where anti-tumor activity of the drug was enhanced [194]. Perhaps more importantly, however, the interaction between chemotherapy drugs and antioxidants is more complex than simply promotion and inhibition of oxidative stress, as both have several mechanisms by which they function [6].

Evidence from systematic reviews

Importantly, a systematic review of 19 clinical trials investigating the use of anti-oxidants including glutathione (7), melatonin (4), Vitamin A (2), Vitamin C (1), Vitamin E (1), ellagic acid (1), N-acetylcysteine (1), and an anti-oxidant mixture (1), found that none of the studies reported evidence of significant decreases in chemotherapy efficacy due to antioxidant supplementation during chemotherapy [19]. This review plus a subsequent systematic review that investigated the question of whether antioxidant supplementation reduces toxicity from chemotherapy [20] reached the conclusions that no trial reported a significant decrease in treatment efficacy and when antioxidants are included in a cancer patient's therapeutic regime:

- toxicity is reduced
- treatment outcomes are improved
- survival times are increased
- tumor response is increased
- the patient is more likely to be able to adhere to the chemotherapy regime.

Table 7.5 Studies of antioxidants and chemotherapy drugs

Antioxidant(s)	Chemotherapy drug	Type of study	Subjects	Outcome
500 mg Vitamin C and 400 mg (600 IU) of Vitamin E for 90 days	Tamoxifam	Humans-clinical trial	Postmenopausal breast cancer patients Treatment group: Vit C and Vit E plus tamoxifam Control group: tamoxifam	Vit E/Vit C treatment associated with significant improvements in lipid profiles, including a significant reduction in triglycerides, and significant increases in HDL and ester cholesterol. This is important since the hepatic estrogenic effect of tamoxifam typically causes severe triglyceridemia [10]
Flavonoids	Epirubicin	In-vitro: cell lines	Chemotherapy-resistant estrogen receptor-negative breast cancer cells	Several flavonoids increased sensitivity to Epirubicin treatment [85]
Vitamin E (600 mg (900 IU) per day	Cisplatin and Taxol	Humans-randomised, open label, controlled (clinical) trial	Treatment group (n = 16): oral Vit E daily during chemotherapy and for 3 months after cessation Control group: no supplementation.	Significant reduction in incidence of neurotoxicity: 25% of Treatment Group compared with 73.3% of Control Group (chemotherapy alone) developed neuropathy during and up to three months after chemotherapy. Relative risk for developing neurotoxicity significantly lower in treatment group compared with controls (RR 0.34) [8]
Curcumin	Taxol	Cell line research and animal study	Paclitaxel (Taxol)-resistant breast cancer cells Breast cancer xenograft model in mice	Cell line research: curcumin enhances the effectiveness of treatment with Taxol Animal study: dietary administration of curcumin significantly decreased the incidence of breast cancer metastasis to lung. It also suppressed the expression of NF-kappaB, COX-2, and MMP9 (matrix metalloproteinase 9) [3]

(continued)

Table 7.5 (continued)

Antioxidant(s)	Chemotherapy drug	Type of study	Subjects	Outcome
Epigallocatechin-3-gallate (EGCG) (Green tea polyphenol)	Taxol	Cell line research	Human head and neck squamous cell carcinoma (HNSCC) and breast carcinoma cell lines that display constitutive activation of HER-2	EECG concentrations of 0.1–1.0 microgram/ml (which are in the range of plasma concentrations after administering a single oral dose of EGCG or a green tea extract) markedly enhanced the sensitivity of both types of cell lines to growth inhibition by Taxol [163]
Vitamin E 300 mg (450 IU) daily	Taxotere and capecitabine combination therapy	Human study (single arm, non-randomised, no control group)	Five breast cancer patients who had developed severe palmar-plantar erythrodysesthesis associated with chemotherapy (hand-foot syndrome).	Significant reduction in symptoms of hand-foot syndrome after one week of Vit E treatment (and no reduction in chemotherapy) [117]
Grape seed extract	Adriamycin	Animal study	Multidrug-resistant breast cancer cell line MCF-7/ADR transplanted into mice	Grape seed extract significantly increased sensitivity of cells to Adriamycin treatment—the combination significantly inhibited tumor growth in mice and reversed the resistance of breast cancer cells to Adriamycin [281, 282]

Conclusions about antioxidants in general

The weight of evidence in the literature supports the contention that antioxidants in general (including low dose dietary forms and high dose IV forms), provide a variety of benefits, do not reduce the efficacy of chemotherapy or radiation therapy, and moreover, that they can increase the effectiveness of conventional cancer therapeutic agents and decrease adverse effects [19, 20, 24, 35, 60, 80]. There is also much evidence that antioxidants slow cancer progression and prevent its spread ([60, 168, 225, 251, 272].

Table 7.5 sets out some studies that demonstrate positive effects of antioxidants on chemotherapy outcomes.

Considering the evidence in relation to individual antioxidants

Different antioxidants may have different interactions with chemotherapy, and this can change with dosage [6], so it is prudent to consider the evidence in relation to them individually. There are also some studies that suggest that some antioxidants should not be combined with particular chemotherapeutic drugs. For example, genestein (an active constituent of soybeans) was found to significantly decrease the effectiveness (in inducing apoptosis) of taxol and vincristine in treating estrogen receptor-positive and negative breast cancer cells [147], yet in combination with the drugs docetaxol, gemcitabine and cisplatin, laboratory research has been found to have a positive effect in sensitizing cancer cells to chemotherapy-induced apoptosis through inactivation of NF-kappaB in multiple cell lines [218]. It is therefore suggested that clinicians check a good drug-supplement interactions database for information. The Integrative Medicine Gateway interactions database (www.imgateway.net) is an excellent clinician's tool which provides evidence-based information on potential interactions between drugs and supplements and western herbs.

Antioxidants and Radiation Therapy

Radiation therapy is used to treat cancer and as a palliative treatment for pain associated with metastatic spread. The primary focus is to increase DNA damage in tumor cells, breaking the double strands of the DNA—this is the direct action of ionization in killing tumor cells. Radiation also works indirectly via the production of ROS in the tissues, altering cellular homeostasis by modifying signal transduction pathways, redox state and sensitivity to apoptosis by the tumor cells [26].

A balance needs to be struck in the use of radiation doses, as there is often collateral damage to nearby normal tissue cells, which can produce side effects for the patient. The extent of danger to normal tissues is dependent on a number of factors including radiation dose, tissue sensitivity, repair capacity, affected organs and the person's endogenous anti-oxidant defences [26]. It is known that as people age, endogenous antioxidants and DNA repair ability decrease, and levels of antioxidants in the cells and blood decrease during exposure to ionizing radiation [26]. The ability of human plasma to protect against ionizing radiation has been

found to be inversely proportional to age [139], suggesting that as people age there may be a higher need for antioxidants to halt oxidative damage [26].

There is increasing evidence that antioxidants such as Vitamin A, Vitamin C and Vitamin E may protect normal cells against some of the side effects of radiation therapy [26, 195] and play a role in sensitizing cancer cells to radiation. Several animal studies demonstrate that Vitamin C with radiation is synergistic, however this has not been studied in humans [61].

Examples of studies that demonstrate a positive effect of Vitamin E in conjunction with radiation therapy are set out in Table 7.6.

However it was also found that a single low dose of dietary antioxidants (that doesn't affect the growth of cancer cells) given just before radiation therapy may protect cancer cells during radiation therapy [195]. What is likely to be missing here is consideration of the beneficial effects of low dose dietary antioxidants on the whole person. Severe illness and aggressive medical therapies deplete antioxidant capacity in collateral tissues. Dosing to prevent this depletion also lessens the effect of medical therapies on non-target tissues, i.e. tissues other than the cancer [61]. Radiation therapy has been found to deplete cellular α-tocopherol in normal cells, and animal studies found that X-ray irradiation decreased tissue concentration of Vitamin C and Vitamin E in bone marrow [247]. Other studies in breast cancer have found that radiation therapy is associated with decreased Vitamin E and selenium, and studies of breast cancer treatment with ROS-producing adriamycine found decreased levels of Vitamin A, Vitamin C, Vitamin E and selenium [26]. The use of antioxidants to protect normal tissue may be very important.

Table 7.6 Studies of vitamin E and radiation therapy

• Vitamin E (400 IU) and Vitamin C (500 mg) have been shown to be effective in improving symptoms and signs in cancer survivors with radiation-induced proctitis including rectal bleeding, diarrhoea and urgency [121]
• In a study of head and neck cancer in humans, Vitamin E (1000 IU) plus pentoxyfylline (0.8 g/day) was found to significantly regress chronic radiation—induced fibrosis [86]
• Vitamin E treatment prior to radiation therapy for glioblastoma multiform may play a role in sensitizing the cancer cells. Vitamin E has been found to induce apoptosis in a dose-dependent manner in glioblastoma cells—exposure for 48 h to 50 μmol/L vitamin E resulted in a 15% increase in apoptosis in the glioblastoma cells [27]
• Vitamin E can selectively increase the apoptotic effect of radiation whilst protecting normal cells from damage in cervical and ovarian cancer cells [128] and neuroblastoma cells [220]
• In mice studies, the synthetic Vitamin E analogue aTOS has also been found to protect against pancytopenia caused by gamma radiation [230] and protect bone marrow [231] as well as inhibit oncogene expression and increase antioxidant enzyme activity [232]
• A study found that high doses of dietary antioxidants that can inhibit the growth of cancer cells (but not normal cells) may enhance efficacy of radiation therapy [195]

Chinese Herbal Medicine

Tumors were recognised in China in the Shang Dynasty (sixteenth–eleventh century BC) where the term 'liu' (tumor) was found on inscriptions on bones and tortoiseshells [142]. The theoretical foundations for the treatment of tumors can be traced back to the earliest recorded book on Chinese medicine, the Huang Di Nei Jing (Yellow Emperor's Internal Classic) [142]. Interestingly, some of the aetiological factors mentioned in the Huang Di Nei Jing included excessive emotions and 'invasion of pathogenic factors' which could only invade when the constitution was 'deficient'. Although such concepts are foreign to westerners, the concept of 'deficiency' here is likely to equate to lowered immune system functioning in biomedical terms, and whilst biomedicine does not recognise external climatic factors in the Chinese medicine sense of this term (for example, an 'attack of wind-cold'), viruses which can cause cancer would fall into the concept of 'pathogenic factors'. Moreover, in Chinese medicine tumors were seen as involving stagnation of qi and blood, qi being a type of life force for which there is no equivalent in biomedicine. In the modern biomedical understanding of the cancer terrain, it is known that the blood supply of tumors can be poor and blood sticky—this equates somewhat with the Chinese medical concept of 'blood stagnation'.

Aetiological Factors

In Chinese medicine, the aetiological factors believed to be associated with cancer include: inappropriate diet, damage caused by emotional factors, depletion or deficiency of the internal organ systems and invasion of external pathogenic factors [142]. This is not too far from those factors that we, in the western world, believe may be associated with cancer: stress/emotions, depleted immune system, hypo-functioning of organ systems, poor diet and in some cancers, viruses.

Chinese Herbal Medicine Treatment of Side Effects of Cancer and Its Treatment

Chinese herbal medicine may be used before, during and after standard cancer treatment (chemotherapy, radiation, surgery) to help decrease the side effects associated with these therapies and aid recovery. For example, Chinese herbal medicines (CHM, combinations of herbs) are able to help address chemotherapy-induced leucopenia. A systematic review that included 83 randomised controlled trials (covering 62 CHMs) found that compared with no treatment, CHMs significantly

decreased the incidence of leucopenia (Odds Ratio −0.23, $p < 0.00001$—this p-value means it was very, very unlikely that this result was by chance). Some Chinese herbs can potentiate chemotherapy and radiation treatment.

Many Chinese herbs have been shown to have anti-cancer properties, acting on many of the pathways involved in cancer, and for these reasons may play a role in the treatment of cancer in conjunction with orthodox medicine. We will look at some of the research shortly. Chinese herbal medicine is also useful in the treatment of many side effects of cancer and its orthodox treatment including, but not limited to the following [142, 186, 242, 265]:

- Xerostomia following radiation therapy
- Nausea, in particular associated with chemotherapy
- Other digestive problems e.g. constipation
- Anorexia
- Polyneuropathy
- Hot flushes
- Anxiety and depression
- Pain
- Insomnia
- Cancer-Related Fatigue.

How Are Chinese Herbs Prescribed?

Chinese herbal medicines are typically prescribed as a medicinal formula, a combination of anywhere between 2 and 12 or more herbs combined according to Chinese medicine principles. Unlike in western herbalism, in Chinese herbal medicine herbs are rarely prescribed as single herbs. The combination of the particular herbs according to Chinese medicine theory helps moderate any potential side effects of herbs, increase the therapeutic effect of the medicinal formula and address additional symptoms and signs that may be present [275].

In Chinese medicine, diseases and disorders are understood to have several underlying subcategories, termed ‘syndromes’ or patterns of disharmony. A syndrome is characterised by particular signs and symptoms that are reflective of the underlying aetiology and pathogenesis of the disease in that person’s body. Chinese herbal medicines (and acupuncture) prescriptions address not only the overarching ‘disease’ but in particular, the underlying pattern of disharmony which may differ from person to person with the same disease diagnosis. The choice of herbs will be quite different for different syndromes. Chinese medicinal formula and acupuncture attempt to treat the root cause of the disease (termed the ‘ben’ or ‘root’) as well as the signs and symptoms (termed the’biao’ or branches, to use the analogy of a tree) [185].

Forms of Chinese Herbal Medicines

Forms of Chinese herbal medicines include the traditional raw herbs (which are boiled up in a clay pot and simmered over heat to reduce the liquid, called 'decoction'), granules, powders, liquid forms, pills and capsules, and, for external conditions liniments and herbal plasters. Hospitals in China may supply patients with the decocted herbs prepared at the hospital, or give them raw herbs to boil up at home, or increasingly, supply granulated herbs (which are dissolved in boiling water) [275] and herbal isolates in tablet or capsule form. Intravenous forms of Chinese herbs are also used in Chinese hospitals also, including the herb Kushen for cancer (for example, Compound Kushen Injection, CKI) and Dan Shen (Radix *Salviae Miltiorrhizae*) for cardiovascular disease.

The Impact of Chinese Herbs on Cancer Pathogenesis

Many Chinese herbs and their active constituents or isolates have anti-cancer properties and impact on various pathways involved in cancer. Some Chinese herbs and/or their isolates can improve patient immunity, and adjust the microenvironment by improving the haemodynamics and blood viscosity to prevent formation of thrombi and micro-metastases of cancer cells whilst others act as anti-oxidants or specifically impact on particular pathways associated with cancer, such as inducing apoptosis or inhibiting angiogenesis [144, 264]. For example, research into isolates has demonstrated that the isolate matrine has been found to inhibit HT29 (colorectal carcinoma cell line) cell growth and influence a large number of gene expressions related to cell proliferation, the cell cycle and apoptosis [97]. Another isolate, allicin is able to enhance the chemosensitivity of colorectal cancer cells (HCT-8 cells) to oxaliplatin: a synergistic inhibitory effect of the combination of the drug and allicin on cell growth was demonstrated which may be related to inhibition of cell proliferation, cell cycle arrest and cell apoptosis [100].

Resistance to chemotherapy is a major obstacle to cancer management, and intrinsic and acquired drug resistance occurs via several mechanisms. The use of polyphenols (and this applies to not only Chinese herbs) as an adjunct to current chemotherapies may improve the therapeutic effects of the drugs and interfere with cancer cell resistance mechanisms [104, 166, 282], as well as reduce unwanted side effects. Chinese herbs and/or their isolates can act synergistically with chemotherapeutic agents. For example, Compound Matrine Injection has a synergistic effect with low dose 5-FU, and was found to strongly inhibit proliferation of colon cancer tumor cells [273]. Paenol, the isolate from Cortex Moutan, is able to inhibit HT-29 colorectal cancer cells alone and at low concentration has synergistic effects with several chemotherapy drugs (including 5-FU, ADM and DDP) in inhibiting proliferation of HT-29 cells [110].

Chinese herbs tend to be prescribed in a medicinal formula and the actions of many of these medicinal formulae have also been studied. For example, it was found that the main constituents of a commonly prescribed pill, Zuojin Pill was able to suppress the proliferation and telemorase activity of HT-29 cells in vitro plus hinder the development and progression of early-stage colorectal cancer [258, 262]. Herbs that are commonly used in cancer supportive treatment include: Huang Qi (Radix Astragali, Astragalus), Xi Yang Shen (Panax Quinquefolius, American Ginseng,), Ling Zhi (G. Lucidum mushroom), Dong Chong Xia Cao (Cordyceps Militaris), Huang Qin (Radix Scuttelarie), Bai Hua She She Cao (Herba Oldenlandia Diffusa), Jiang Huang (Rhizoma Curcumae Longae, Turmeric Rhizome) and Ban Zhi Lian (Herba Scutellariae Barbatae, Barbat Skullcap) [264].

Scientific Evidence of Chinese Herbal Medicine in Cancer Treatment

Research has been conducted into Chinese medicinal formulae, single herbs, and the active constituents of the herbs. In practice, most Chinese medical practitioners will prescribe medicinal formulae according to the underlying pattern of disharmony presenting in the patient with cancer. However, many herbs that are known to have anti-cancer actions either historically or through modern research are also included in Chinese medicinal formulae precisely for these anti-cancer actions.

Whilst Chinese medicine practitioners may focus on prescribing medicinal formulae, the knowledge from the scientific research perspective of how the single herbs and isolates might work brings an important level of evidence to justify choice of herbs. Research into single herbs, single isolates and combinations of isolates may facilitate confidence in other appropriately-trained integrative medicine practitioners in the prescribing of Chinese herbs, for example, isolates or combinations of isolates in tablet or capsule form. Chinese medicine practitioners may also choose to add Chinese herbal isolates to their treatment regimes, adding another dimension to their practice.

A focus on isolates has some limitations however. The drug discovery model seeks to isolate the active constituents of plants, and this has been successful for a handful of herbs: for example, artemisinin isolated from the herb Qing Hao (sweet wormwood) and its synthetic derivatives are used as anti-malarial drugs. The key point is that strength of Chinese herbal medicine is understood to lie in the combination of herbs, chosen according to Chinese medicine theory, that have the ability to address the root cause of the illness and its signs and symptoms. It is the synergism between herbs and, drilling down further, the potential synergism between the many active constituents within and between the herbs in a formula, that is likely to be responsible for the therapeutic effect. So, reductionist attempts to focus only on active constituents of an herb may miss what is likely to be the real strength of Chinese medicine, the judicious combination of herbs. The field of omics provides

potential tools to understand how combinations of herbs and isolates may impact on the body's systems. Therefore, research needs to look at all possibilities—isolates, combinations of isolates, whole herbs, and combinations of herbs.

Examples of research evidence in relation to the impact on the cancer terrain of several Chinese herb isolates is set out in Table 7.7 as an illustration. For a comprehensive understanding of the action of isolates from Chinese herbs and their use in oncology, readers are referred to the book by Professor Daniel Weber PhD, Botanical Oncology: Isolates [264].

Examples of research evidence in relation to the effect on the cancer terrain of a small selection of Chinese medicinal formulae is set out in Table 7.8, again to illustrate the kinds of research that has been conducted in the field of oncology.

Intravenous Chinese Herbs

IV Artemesinin

Chinese herb Qing Hao, Artemisis annua or sweet wormwood, had a long history of use as an anti-malarial herb in ancient China. The use of the crude herb has been replaced by various preparations of its active constituents, the most well-known being Artemisinin and two synthetic derivatives, artemether and sodium artesunate [212]. Artemisinin contains an endoperoxide moiety that reacts with iron to form cytotoxic free radicals. Since iron influx is high in cancer cells, artemisinin is able to selectively kill cancer cells in vivo [133, 228]. The semi-synthetic derivative of Artemisinin, artensuate has been found to be cytotoxic to several cancers including some that are drug resistant, in particular against leukemia and colon cancer cell lines [212].

In vitro research has demonstrated that a combination of artemisinin and holotransferrin selectively killed human leukemia cells but was much less toxic to normal lymphocytes [132]. The combination was significantly more effective than either alone [132]. Transferrin is transported into cells via endocytosis, and once inside releases its iron. Cancer cells over-express cell surface transferrin receptors for iron uptake compared with normal cells (which express almost undetectable levels) [179]. Artemisinin covalently tagged to transferrin is endocytosed into cancer cells as a pro-drug and has been shown to induce apoptosis in prostate cells [179] and, in a rat model of breast cancer, significantly retard tumor growth rate [134].

IV Ku Shen

Intravenous Kushen Injection (CKI) has been used in China for over 15 years to treat several different types of solid tumors [202], and has been used either alone or in conjunction with chemotherapy and radiation therapy in cancer treatment including the treatment of cancer-related pain [84, 274]. CKI consists of two Chinese herbs, Ku Shen (Radix Sophorae Flavescentis) and Baituling (Rhizoma simlacis Glabrae), and each has a number of active constituents [202].

Cancer stem cells (CSCs) are believed to be involved in oncogenesis, cancer relapse and metastasis, as they are resistant to conventional cancer therapies

Table 7.7 Chinese herb isolates and their impact on the cancer terrain [264]

Chinese herb isolate	Isolated from	Cancers	Anti-cancer actions	Research findings
Artemisinin	Qing Hao [Artemisia Annua (L.)]	Breast, gastric cancer, leukemia [264]	Five key pathways: PI3K-Akt, T cell receptor, Toll-like receptor, TGF-beta and insulin signalling pathways [98]	In rat experiments, Artemisinin significantly delayed or prevented breast cancer development, and in rats fed artemisinin, breast tumors where significantly smaller and fewer [135] Artemisinin inhibited growth and modulated expression of cell-cycle regulators in gastric cancer cells, as well as led to an increased expression of p53 [284] Artemisinin is known as an anti-leukemia agent and has been found to strongly enhance the action of low doses of 1α,25-dihydroxyvitamin D3 and all-trans retinoic acid in leukemia cell differentiation [122]
Baicalin and baicalein	Roots and leaves of several Chinese herbs including Scutellaria Radix, Scutellaria Baicalensis (Georgi), Scutellaria Rivularis (Benth.), and Scutellaria Lateriflora (L.)	Liver, colorectal, prostate, breast, oral, liver, myeloma, ovarian [264]	Anti-cancer, cytostatic, anti-inflammatory, anti-oxidant, anti-angiogenic, neuroprotective, cardio-protective (against doxorubicin), inhibits cell invasion and migration [264]	Shows almost no or minor toxicity to normal epithelial cells and normal peripheral blood and myeloid cells [264] Baicalin decreased the expression of VEGF, cMyc and NFkB and Baicalein was found to decrease expression of VEGF, HIF-1α, cMyc and NFkB in ovarian cell lines, suggesting that they both significantly inhibit the viability of ovarian cancer cells [42] Baicalin potentially inhibits proliferation of human breast cancer cells, in particular mammary cell line MCF-7 and ductal epithelial tumor cell line T-47D proliferation [70] Cell research has demonstrated that Baicalein, derived from Scutellaria baicalensis, induced apoptosis via Akt activation in a p-53 dependent manner in HT-29 colon cancer cells [124]

(continued)

Table 7.7 (continued)

Chinese herb isolate	Isolated from	Cancers	Anti-cancer actions	Research findings
Emodin	Chinese herb Da Huang (Rheum Palmatum L), Polygonum Multiflorum plus other herbs	Breast, colon, liver, myeloma, oral, pancreatic, liver, lung, leukemia, chemotherapy [264]	MDR-1, cell cycle arrest, anti-inflammatory [264]	Emodin has a synergistic effect with several chemotherapeutic drugs- it was found to substantially enhance cytotoxicity of 5FU, MMC and MTX against human hepatoma BEL 7402 cells. It also partly reversed the multi-drug resistance in human breast cancer cells (MCF7/Adr cells) [112] Aloe-emodin was found to enhance radio-sensitivity when used in conjunction with radiation therapy. Aloe-emodin and radiation in combination induced apoptosis, upregulated cyclin B and γ-H2AX expression and further improved ALP activity compared with treatment with either alone [155] Emodin and aloe-emodin are capable of inhibiting breast cancer cell proliferation by down-regulating ERα protein levels, thereby suppressing ERα transcriptional activation [99]
Ginsenoside	Xi Yang Shen (American ginseng, Panax Quinquefolium) Ren Shen (Chinese Ginseng, Panax Ginseng) San Qi (Panax Notoginseng)	'Breast, colorectal, brain, acute myloid leukemia, melanoma, lung, glioblastoma, prostate, fibroblast carcinoma' [264, p. 207]	'Multi-drug resistance, apoptosis, anti-cancer, chemotherapy sensitizer, CYP450 regulating, inhibits growth and metastasis, down-regulates MMP-9, enhances 5-FU, anti-inflammatory' [264, p. 207]	Ginsenoside Rg3 has been found to inhibit angiogenesis and cell proliferation in glioblastoma. Rg3 has been found to increase glioblastoma cell apoptosis via the MEK signalling pathway and reactive oxygen species [44] Rg3 has been found to sensitize prostate cells against chemotherapy; a combination of Rg3 plus docetaxel was more effective than either docetaxel or Rg3 alone in inhibiting cancer cell growth and inducing apoptosis and g(0)/G(1) arrest with a significant inhibition of NF-kappa B activity [123]

Based on data from Weber [264]

Table 7.8 Research into some Chinese medicinal formulae used in cancer treatment

Name of formula	Herbal constituents	Research findings
LCS101 formula	Astragalus Membranaceus [Huang Qi], Poriae Cocos [Fu Ling], Atractylodes Macrocephala [Bai Zhu], Lycium Chinense [Gou Qi Zi], Ligustrum Lucidum [Nu Zhen Zi], Paeonia Lactiflora [Chi Shao Yao or Bai Shao], Paeonia Obovata [Mu Dan Pi], Citrus Reticulate [Chen Pi], Ophiopogon Japonicas [Mai Men Dong], Milletia Reticulate [Ji Xue Teng], Oldenlandia Diffusa [Bai Hua She She Cao], Scutellaria Barbata [Ban Zhi Lian], Prunella Vulgaris [Xia Ku Cao], and Glehnia Littoralis [Sha Shen]	20 female breast cancer patients were treated with LCS101 as an adjuvant to conventional chemotherapy. At the end of treatment 70% reported that they had either no or mildly severe levels of fatigue; 60% had none to mildly severe weakness; 85% had none to mildly severe pain; 70% had none to mildly severe nausea; and 80% reported none to mildly severe vomiting. Results indicated that 20% reported severe impairment of overall function, 40% severely impaired Quality of Life and 85% reported that they believed the botanical compound helped reduce their symptoms. No toxic side effects were attributed to the LCS101 treatment by the study [216]
Kangai injection	Key herbs: Astragalus [Huang Qi], Ginseng [Ren Shen], oxymatrine: extracted from Sophora Flavescens [Ku Shen]	The efficacy of Kangai injection plus chemotherapy versus control (chemotherapy) was investigated in 80 patients with advanced gastric cancer. In the treatment group NK cellular activity and CD4/CD8 ratio was significantly higher after treatment, and CD3 and CD4 were increased. There was significantly less leukopenia, nausea and/or vomiting and peripheral nerve toxicity, in the treatment group compared with the control group. There was less fatigue, better appetite and Karnofsky score was significantly increased in the treatment group. Treatment was significantly more effective in relieving pain and assisting patients to gain weight compared with the control medication. The authors concluded that treatment of advanced gastric cancer with Kangai injection in conjunction with chemotherapy may reduce the negative impact of chemotherapy on the patient's immune function and reduce side effects, thereby improving quality of life [271]

(continued)

Table 7.8 (continued)

Name of formula	Herbal constituents	Research findings
Fu Zheng Pai Du Kang Ai Fang (formula for supporting Vital Qi, expelling toxins and inhibiting cancer)	Key Herbs: Huang Qi (Radix Astralagus Seu Hedysari), Huang Jing (Rhizoma Polygonati), Ren Shen (Radix Ginseng), Xian He Cao (Herba Agrimoniae Pilosae), Yu Xing Cao (Herba Houttuyniae Cordatae), Da Huang (Radix Et Rhizoma Rhei), Shu Ling (Sclerotium Polypori Umbellati), Ban Bian Lian (Herba Lobeliae Chinensis Cum Radice), Bai Hua She She Cao (Herba Heyyotidis Diffusae), Tian Nan Xing (Rhizoma Arisaematis), Yi Yi Ren (Semen Coicos Lachryma-jobi), Tao Ren (Semen Persicae), Gua Lou (Fructus Trichosanthis), Xia Ku Cao (Spica Prunellae Vulgaris)	Non-small cell carcinoma study: 63 patients randomized to receive chemotherapy plus Chinese herbal medicine (CHM) and 51 received chemotherapy only. Results showed that the CHM plus chemotherapy group performed significantly better than the chemotherapy group in terms of weight loss, nausea and vomiting, decrease in Hb, decrease in WBDs, and decrease in platelets [140]

including advanced targeted therapy. CSCs have been identified in several cancers including leukemia, breast, prostate, gastrointestinal and brain cancers [274]. Research has demonstrated that CKI is able to suppress the size of CSC-like cell population by approximately 90% and down-regulate the main genes of the Wnt signalling pathway (upregulation of the Wnt signalling pathway correlates with tumor progression) [274].

CKI has several other actions on the cancer terrain. CKI has been shown to regulate immune function, synergize the therapeutic effects of chemotherapy and radiation therapy, and can induce apoptosis and inhibit migration, invasion and cell-adhesion ability by downregulating the expression of $CD44_{v6}$ protein [274]. CKI also has anti-inflammatory, anti-allergic, antiviral, and anti-fibrotic activities [84]. It has been shown to inhibit growth and induce apoptosis of MCF-7 breast cancer cells, and to alter the expression of clinically relevant cancer genes. Several important genes were significantly upregulated when cells were treated with CKI but not the chemotherapy drug 5FU, and genes that are involved with cell growth or are biomarkers of carcinogenesis were significantly down-regulated. CKI may also down-regulate IncRNA H19 which is overexpressed in many cancers; many of the INcRNAs are important gene regulators in the cancer pathway [202].

A systematic review of 16 trials (1564 patients) found that the total pain relief rate of CKI plus chemotherapy was better than chemotherapy alone except for colorectal cancer, and CKI plus chemotherapy was associated with a significantly lower incidence of leukopenia, and gastrointestinal, hepatic and renal functional lesions. This suggests, indirectly, that CKI is able to reduce the toxicity of the chemotherapy drugs [84].

Acupuncture

Acupuncture involves the insertion of fine needles into acupuncture points located along meridians, pathways in which the Qi of the body is believed to circulate, as understood in Chinese medicine theory. There are 14 main meridians traversing the surface of the body, and over 365 acupuncture points, each of which has typically two or three therapeutic actions. There are also microsystems such as the ear, in which the body is mapped onto the surface of the ear. In auricular acupuncture, needles are therefore inserted into the ear. Chinese medical acupuncture is guided by Chinese medicine theory and differs from ‘dry needling’ which uses trigger points and is primarily used to treat musculoskeletal problems such as pain and stiffness.

Acupuncture may be used as an adjunct treatment for improving general well-being as well as alleviating many of the side effects of cancer and its orthodox treatment with surgery, chemotherapy and radiation therapy. This includes treatment of pain, nausea, vomiting, anxiety, depression, hot flushes, fatigue, insomnia, neuropathy and in the case of radiation therapy, xerostomia [182, 186, 188, 242].

Research indicates that acupuncture used in conjunction with chemotherapy can alleviate many side effects. A clinical trial in which cancer patients were given acupuncture the day before, the day of, and the day after chemotherapy demonstrated significant reductions in pain, nausea, vomiting, insomnia and anxiety compared to baseline [242]. Acupuncture has also been shown to assist in the treatment of insomnia [186].

Acupuncture may be used in conjunction with radiation therapy to alleviate serious side effects such as xerostomia which can severely impact on patients' quality of life. A randomised controlled trial demonstrated that acupuncture applied three times a week on the same days as radiation therapy is effective in preventing the development of xerostomia (dry mouth), one of the very troubling side effects of radiation therapy applied to the head and neck [164]. Positive effects on subjective symptoms were seen as early as three weeks into treatment, and significantly greater salivary flow in the acupuncture treatment group compared to the control group was seen at 7 weeks. The positive effects continued through to 6 months after the completion of radiotherapy [164]. Other studies have found that application of acupuncture is effective in relieving xerostomia including xerostomia post-radiation therapy [21, 22, 57], and additional acupuncture post-radiation therapy has been found to maintain the improvement in salivary flow rates for up to three years [22].

It is important that acupuncture is performed by practitioners who are adequately trained.

Promising Technologies and Therapies

Hyperthermia

The use of heat to treat cancer has been around for several centuries [213, 224]. Its early history was characterised by observations by several doctors in the late 1800s that some cancer patients underwent spontaneous remission after contracting erysipelas and the attendant prolonged fever. Readers are referred to Roussakow's paper for a nice potted history [213].

Hyperthermia involves the elevation of the body's temperature above normal physiological levels, typically in the range of 39–45 °C, to achieve a therapeutic gain [253]. Hyperthermia may be administered invasively or non-invasively, and involves exposing tissues to conductive heat sources or non-ionising radiation—electromagnetic or ultrasound. Hyperthermia may be localised, regional (perfusion hyperthermia) or applied to the whole body [253].

Local hyperthermia aims to deliver the optimal thermal dose to the tumor without damaging the surrounding normal tissues. It may be applied via external, intraluminal or interstitial methods. Perfusion hyperthermia is used to treat a region, such as a limb, organ or body cavity. Whole body hyperthermia aims to introduce energy into the body whilst minimising energy losses. Temperatures are usually

limited to 41.8–42 °C. There are several methods, some requiring deep sedation in combination with radiant heat, however there is a newer approach that uses a lower temperature of 40° in combination with cytokines and/or cytotoxic drugs for a longer duration [253].

Hyperthermia is often used as an adjunct to radiation therapy and chemotherapy. Reviews of the literature suggest that there is a growing body of level 1 evidence (obtained from at least one properly randomised controlled clinical trial) indicating that hyperthermia is efficacious as an adjunct to radiation therapy and chemotherapy in a range of cancers. Where clinical studies have failed to show a benefit, several were found to have used inadequate heat to be able to achieve a therapeutic effect [253].

Sono Photo Dynamic Therapy (SPDT)

Sono Photo Dynamic Therapy (SPDT) is a new method that combines photodynamic therapy (PDT, which was first approved by the FDA for certain kinds of cancer in 1998) and sonodynamic therapy (SDT), a new modality that uses ultrasound to treat cancer. The basic PDT technology was originally developed in Ireland, and this technology was further developed in China into what became SPDT, with the addition of the ultrasound and use of chorophyll-derived oral sensitizers to sensitize the cancer cells to light and ultrasound.

SDT (alone) works on the principle of using ultrasound-dependent enhancement of the cytotoxic activities of a sonosensitizer, to produce free radical oxygen to kill cancer cells [107]. Animal studies have confirmed that the oral sensitizing agents are preferentially taken up by cancer cells and not by normal cells [143]. Thus, the sonosenitizer is introduced to the body and it accumulates in the cancer cells, but not normal cells. Ultrasound is able to pass through the body, destroying the cancer cells, with the added advantage of also being able to destroy metastases in most parts of the body [107]. PDT, on the other hand, uses light—again a photo-sensitizing agent is used which accumulates in the cancer cells, however its ability to penetrate deeply into the body is not strong.

There are currently only a few clinics around the world offering this combined therapy, (SPDT) including one in Guangzhou, China and in Japan. In Guangzhou, SPDT is often used in conjunction with low-dose chemotherapy, and oxygen therapy, and integrates Chinese herbal medicine and oral/dietary vitamin supplements (IV vitamins are not allowed in China, unlike other countries such as Australia and the US).

In vitro and animal research

There is a substantial amount of research in cell lines and animals on SDT and PDT. For example, ultrasound in conjunction with photo-chemically active chlorophyll was shown to be able to induce apoptosis and necrosis in Human promyelocytic leukemia (HL-60) cells [279]. Research indicates a synergism

between ultrasound therapy and conventional therapies. For example, in vitro experiments have also demonstrated that SDT is synergistic with chemotherapy [143] and with non-steroidal anti-inflammatory drugs tenoxicam and piroxicam (the antitumor effects of ultrasound were enhanced by these two drugs) [214]. SDT in combination with a sono-sensitizing agent was found to be able to inhibit the growth of sarcoma in mice and that the inhibitory effect was sound intensity-dependent. The results also indicated that SDT induced an inflammatory reaction, suggesting a 'vaccine' effect, and that it was able to penetrate bone to reduce tumors [261].

Clinical data: case studies

The clinical data in support of SPDT at this point in time is in the form of case studies, including cases of women with advanced refractory breast cancer who had failed to respond to conventional therapy, and who achieved partial or complete responses to the SPDT [262]. Case studies in seven patients with advanced esophagocardiac and gastric adenocarcinoma who underwent SPDT and concurrent chemotherapy indicated an overall response rate of 85% with three achieving complete responses and three achieving partial responses. The main side effects which were reversible were mild pain in tumor areas, tiredness and weakness [143]. The use of oxygen therapy, incorporated in the Guangzhou SPDT clinic, has been found to reduce the fatigue that can follow SPDT (believed to be due to release of cytokines and other inflammatory mediators when the cancer cells die).

Australian clinical research in prostate cancer

Australian research conducted at the National Institute of Integrative Medicine investigated the use of sono- and photo-dynamic therapy in the treatment of prostate cancer. The laser and ultrasound probes were directed at the prostate in a combination of trans-rectal, trans-urethral and per-cutaneous techniques. Treatment was twice daily for three days over one week, with this protocol repeated twice in 12 weeks. After more than 6 months post-treatment, Prostate-Specific Antigen (PSA) was either stable or decreased in 17/31 patients. Of the remaining 14 patients who had an increased PSA, 9/14 had a positive prostate biopsy and negative bone/CT scan, 3/14 had a negative biopsy, and 2/14 had positive lymph nodes on abdominal CT scan [177]. The study indicates that over 50% of the study participants responded positively to the therapy, suggesting that this combination of photo and sono-dynamic therapy may hold promise.

Circulating Tumor Cell (CTC) Diagnosis

Circulating tumor cell (CTC) detection is an important adjunct to integrative oncology practice. CTCs are tumor cells that are shed from primary tumors and are carried around the body via the bloodstream. The isolation of CTCs has allowed the cells to be grown in the laboratory and their genetic mutations analysed, as well as response to various drugs investigated [278]. CTCs are associated with early

carcinogenesis [105] and an increase is associated with cancer progression [53], whilst a decrease is associated with disease containment or remission [94]. CTC levels may provide a biomarker for disease progression and treatment effectiveness. CTC screening is advisable for those who are at increased risk of malignancy, for example history of Hormone Replacement Therapy, smoking, and family history of cancer [210].

There are several techniques available to identify CTCs including ISET (Isolation by Size of Epithelial Tumor) which uses filtration and microscopic analysis using standard histopathological criteria. This technique has been validated and shown to provide 100% specificity (1 CTC/ml) and sensitivity (0 CTC/ml in 600 healthy donors [95, 256].

The value of the ISET CTC test has been demonstrated first hand at the National Institute of Integrative Medicine in Australia. Between September 2014 and September 2015, 310 ISET screening test were conducted, 150 of which were CTC screening requests. Of these 150, CTCs were detected in 80 (58%). Follow-up CTC test results or scans were available for 11 of these. These 11 patients were divided into three groups:

- Group 1: $n = 5$, no tumor detected initially, 3 months of adjuvant treatment, CTC test before and after adjuvant treatment
- Group 2: $n = 4$, no tumor detected initially, no adjuvant treatment, CTC test before and 3 months later
- Group 3: $n = 2$, tumor detected initially, CTC before and after 3 months' adjuvant treatment.

The adjuvant therapy included diet and lifestyle advice, plus a range of supportive supplements to boost the immune system including NK cells, suppress Ras oncogene expression, inhibit cyclooxygenase enzymes, inhibit angiogenesis, correct coagulation abnormalities, maintain bone integrity, inhibit 5-lipoxygenase (5-LOX) enzyme and inhibit cancer metastasis. The supplements included mushroom extracts, Vitamin D, vitamin K, vitamin B12, probiotics, fish oil, Kyolic aged garlic extract, curcumin, boswellia, and green tea extract [210].

Results indicated that in Group 1, CTCs were reduced within an average of 5 months using adjuvant therapy, whilst in Group 2 (positive CTC test but no tumors initially), follow-up scans revealed tumors in lung ($n = 1$), breast ($n = 2$) and prostate ($n = 1$). In the two patients who had a positive CTC test and positive scans for tumors, CTC testing post-adjuvant therapy revealed a reduced CTC count [210]. Whilst only a very small study, it showed clearly the value of CTC screening in early detection of cancer—those four people who had no tumors initially but had detectable CTCs soon had them. It also showed the value of the adjuvant therapy in lowering CTCs. It certainly provides the basis for the conduct of larger scale studies of this nature.

Immunotherapy with GcMAF and Colostrum MAF

Cancer immunotherapy uses the body's own immune system to help fight cancer. One such strategy involves activating the immune system to recognize and attack tumor cells [238]. A relative newcomer to the field of cancer immunotherapy that shows promise is Gc protein-derived macrophage activating factor (GcMAF), also known as vitamin D binding protein-macrophage activating factor (DBP-MAF). It is a potent endogenous macrophage activating factor (MAF) found naturally in the blood at low concentrations. GcMAF has several biological activities including macrophage activation via superoxide radical generation, phagocytic activation, and anti-tumor and anti-angiogenic activities [108].

Whilst the first-generation and second-generation GcMAF were developed from human serum and used as an injection, another MAF was also developed in 2014 by Saisei Mirai in collaboration with Tokushima University in Japan, using bovine colostrum. This new form, referred to as Colostrum MAF, is administered orally in an acid-resistant enteric capsule in order to activate macrophages in the gut-associated lymph tissue [106, 107]. The powder within the capsule may be administered sublingually, and can activate macrophages in the lymphoid tissue of the mouth and throat [106, 107]. There is now also a liquid in spray form.

The goals of these immunotherapies are to improve general wellbeing and quality of life, increase the number of monocytes and activate macrophages to destroy cancer cells, viruses, bacteria and other pathogens, and increase the rate of maturation of dendritic cells [106]. Gc MAF and Colostrum MAF have applications beyond cancer, including treatment of multiple sclerosis [108], chronic fatigue syndrome (CFS) and infectious diseases [106] that have also been reported. Patients taking oral Colostrum-MAF have also reported improvement in skin condition [106]. Other case studies presented at scientific meetings (not currently published) indicate it may also be useful in the treatment of alopecia, atopic dermatitis, pollinosis, rheumatoid arthritis, chronic actinic dermatitis (personal communication Sasei Clinics, Osaka, Japan, 28 October 2016).

Case studies indicate that Colostrum MAF may have an important role in palliative care including the treatment of infections which can severely compromise quality of life, and also be used to address CRF, a common affliction in cancer patients [106]. Purified GcMAF, serum GcMAF and Colostrum MAF increases phagocytosis but does not cause production of cytokines [249]—this is relevant as it is believed by some researchers that fatigue can be caused by chronic cytokine production when macrophages are activated by lipopolysaccharide (LPS), an endotoxin from gram-negative bacteria [106].

A recent case study combined the use of sonodynamic therapy (SDT) using low-intensity ultrasound and tumor treating fields (TTF) therapy (another novel therapy where continuous low-intensity, intermediate-frequency alternating electric fields are applied to the region(s) of the tumors), ozone therapy (to improve local hypoxia within the tumor environment which should enhance the SDT) and second generation GcMAF and oral Colostrum MAF in a 77 year old male with non-small

cell lung cancer (Stage 3B). Results indicated that the tumor marker neuron-specific enolase (NSE) decreased to within normal limits and the CT scan indicated necrosis of the tumor, and no increase in the tumor size was found 15 months later. Importantly, the patient's other symptoms improved by taking the oral Colostrum MAF, with better sleep quality, less nocturia and more energy reported [107].

Mechanisms of action

The exact mechanisms by which GcMAF and Colostrum MAF work and their clinical indications are still being elucidated. Macrophages display phenotypic plasticity and heterogeneity and there are several macrophage subtypes that respond differently to the various MAFs [238]. Importantly, there are different types of macrophages found all over the body and the method of administration and type of MAF used varies. Macrophage activation with GcMAF does not result in nitric oxide, tumor-necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) production, unlike activation by LPS. It is thought that because of the apparent greater affinity for activation of macrophages by GcMAF compared with LPS, administration of exogenous GcMAF can suppress LPS-related macrophage activation and therefore induce phagocytosis without the release of pro-inflammatory cytokines such as TNF-α and IL-1β [106].

Much of the research is laboratory based at this time, and whilst it is easy to dismiss case studies as being inferior to RCTs, they are nonetheless a clinically relevant form of evidence. As case studies gather in number, they often begin to show patterns. Clinical trials are not far off. This will be an interesting therapy to watch as the clinical research evidence develops.

Conclusion

In addition to advice about stress, nutrition, sleep, sunlight and Vitamin D, and exercise, there are many additional therapies that may assist people living with cancer. These include the use of supplements where diet may be deficient, and it can also include the use of western herbal medicine, Chinese herbal medicine and acupuncture to help improve the immune system functioning, assist general well-being, and help alleviate some of the effects of cancer and side effects of its orthodox treatment. There are several innovative therapies that also show promise as adjuncts to orthodox treatment, including hyperthermia (which is one of the older adjunct therapies), newer therapies such as PSDT and novel products like Gc-MAF.

It's worth remembering that novel technologies and products will nearly always threaten the status quo and anything outside of orthodox medicine is often viewed with suspicion. Also, research funding is difficult to come by in the field of integrative medicine and so it takes little longer when there is less money available to establish the gold standard of scientific evidence. This is really where we need our

governments to help out. Research into integrative approaches, as exemplified by Dean Ornish's excellent research that investigated the efficacy of a lifestyle approach in coronary heart disease [189] provides a good example of research that is useful for clinicians.

We have only covered a few of the additional therapies that may be incorporated in a holistic patient Wellness Plan, discussed in Chap. 8. There are many others such as chiropractic (for example to assist after surgery where skeletal muscle may have been damaged), homoeopathy and Bach flowers or Australian Bush Flower Essences (useful in particular for dealing with the emotional aspects of living with cancer), massage (useful for relaxation and stress relief as well as recovery post-surgery), to name a few. At the National Institute of Integrative Medicine in Australia, in addition to integrative (western) medical practitioners, we have several allied health practitioners in our team including practitioners of naturopathy, nutritional medicine, Chinese medicine, homoeopathy, myotherapy, chiropractic, and psychology. We also offer hyperthermia (localised, regional, whole body), IV vitamin therapy and CTC analysis. We conduct research into integrative medicine and provide education to practitioners and the public. Our centre, like others around the world, are modelling an integrative approach to health that integrates the best of evidence-based western medicine and other forms of allied health/complementary medicine.

Additional Reading

Giving GSH to Cancer Patients—Yes or No?

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Introduction

GSH (glutathione) in cancer therapy is controversial. In some human clinical trials GSH therapy has been associated with decreased toxic side effects of various chemotherapy drugs without decreased effects of the drug. In some cases, the effect of the drug is increased. Other human clinical trials have shown less benefit but consistently have *not* demonstrated a decreased response from chemotherapy drugs. Of course not every drug or cancer has been tested; this is the case for *any* drug. But at this stage there is no human clinical literature that shows that GSH administration in cancer patients has negative outcomes.

No human clinical trials have studied Vitamin C and GSH in combination in cancer. One animal study has looked at this; very high dose GSH did reduce the objective effect of Vitamin C on implanted tumors. But all surviving animals in various groups after a set time were euthanized and the group at this time with the highest number of survivors was the Vitamin C + GSH group. So there was increased survival in the animals treated with the Vitamin C and Glutathione. Significantly this reduction in the decreased growth rate of the tumors by glutathione required an adult human body weight equivalent of 40–70 g of glutathione —an amount well outside levels routinely used in cancer studies (discussed later in this dissertation).

In stark contrast, most in vitro trials on GSH demonstrate increased resistance to some chemo drugs with high intracellular GSH levels, in particular associated with high expression of Glutathione transferase (GST) enzymes, in particular some identified types of GSTs or their mutations in various cell lines. High expression of some GSTs has been associated with increased risk for some cancers and poor outcome in some cancers. However GSH levels in various cancers or systemically has been studied in humans with reference to prognosis and survival. Prognosis for some cancer types is better when cell GSH levels are higher.

Overall no consistent relationship has been found between tumor GSH levels and survival.

The goal of adjunct GSH therapy in cancer treatment is to support the total antioxidant capacity of the patient and in general to assist with quality of life and side effects from medical interventions.

No human clinical literature to date demonstrates that these goals are adversely affected by administration of supplemental GSH or that drugs are adversely affected, or that the prognosis of the cancer patient is adversely affected.

Results from in vitro or animal trials in general cannot be extrapolated to clinical outcomes in humans. This information can only be gleaned from cases and human trials. In both cancer cases and clinical trials GSH adjunct therapy has not yet been demonstrated to have detrimental effects.

Clinical Trials

Numerous clinical trials combining GSH and chemotherapy have been conducted. The majority of these are positive, and none show antagonism with the drug or patient [24, 36, 62, 146, 169, 234]. GSH therapy does not interfere with the drug, the dose limiting toxicity of the drug is improved and side effects are reduced. Most studies are with platinum drugs and 5-FU. Only one trial by Leal et al. [137] did not find significant benefit from adjunct GSH. No human clinical trials have shown GSH drug interference, at worst there was no change in drug effectiveness or no effect overall.

GST Mutations and GSH Levels in Cancer Patients

Many cancer cell lines exhibit high expression of a variety of GST enzymes. Treatment with chemotherapy can further induce these genes and lead to even higher expression and drug resistance. GSH is typically used as the reducing power for GST enzymes; high intracellular GSH levels are related to drug failure in numerous cancer cell lines—most but not all in vitro studies find this. Also whilst some clinical studies show an inverse relationship between patient survival and *tumor* GSH, others find no relationship with *tumor* GSH. For example, Gamcsik and colleagues [74] state:

- "Glutathione tends to be elevated in breast, ovarian, head and neck, and lung cancer and lower in brain and liver tumors compared to disease-free tissue. Cervical, colorectal, gastric, and esophageal cancers show both higher and lower levels of tumor glutathione".

In breast cancers, no differences in disease-free or overall survival were noted in patients with high levels of glutathione in tumors [29]. In fact, high levels of glutathione in tumors were associated with good prognosis and low levels were associated with more aggressive or more advanced disease [29]. Woolston and colleagues [269] found no correlation between glutathione levels and recurrence or overall survival in breast cancer. There is mixed results in the literature in relation to levels of GSH in tumors and histological grade of tumor in breast cancer [74].

High systemic GSH levels in some studies are positively related to survival [54]. Crohns and colleagues [54] found:

- "Higher levels of baseline plasma thiols were associated with better overall survival. We noted in this study that the patients' overall survival was longer if baseline plasma thiols were above the median. A recent study showed that head and neck cancer patients with a higher than median glutathione value survive longer than those whose value is below the median".
- "The concentrations of the most important antioxidants are reduced in the blood during chemotherapy, probably because antioxidant defense mechanisms are activated to combat the free radical storm produced by the chemotherapy. Different oxidative stress markers seem to behave differently in this respect. Repetitive polychemotherapy with radical-generating compounds may exceed the antioxidant capacity of cancer patients and lead to high oxidative stress. This study also suggests that higher baseline thiols may predict better overall survival".

In tumors that already have high GST expression and high GSH levels it is unknown what effect exogenous GSH will have on these levels. However it is the *tumor cells* that have the high levels, not the patient's other tissues. Since the levels in some cancers are already high, and that maintenance of these levels is due to the disrupted machinery of the cancer cell, it is unlikely that exogenous GSH will have

much impact on this. Exogenous GSH would be expected to mostly raise the ailing levels in the non-cancer tissues in the patient, particularly if they are undergoing toxic therapy, and supplementation with glutathione would be expected overall to aid the quality of life of the patient. In the preceding GSH and chemotherapy clinical trials this is exactly what exogenous GSH does, in some cases also leading to greater efficacy of the drug/s.

GSH with Vitamin C

No human clinical trials have been conducted with a Vit C/GSH combination. Cases have not been published however amongst physicians treating cancer patients there have been many cases using combination therapy. As such, published data is not accessible about these combinations. However clinical comment extrapolated from in vitro trials is not appropriate as it often bears no relation to response in humans. In vitro trials on antioxidants are notorious for being wrong, a topic discussed in length at the end of this review.

GSH and Vitamin C: Animal Trials

Only one trial exists to date, that of Chen and colleagues [39]. The study conducted both in vitro and tumor xenograft tests in mice. The conclusion published with this trial states:

- "These data confirm the pro-oxidative anti-cancer mechanism of pharmacologic AA and suggest that AA and GSH administered together provide no additional benefit compared with AA alone. There is an antagonism between ascorbate and glutathione in treating cancer, and therefore iv AA and iv GSH should not be co-administered to cancer patients on the same day."

This is not a clinical trial but makes a strong clinical recommendation.

A comprehensive response has been published to the Chen et al. [39] paper by Dettman and Meakin [60]. Of particular interest are the following issues in relation to the Chen et al. [39] study:

- Mice implanted with pancreatic tumors were treated for 18 days with intraperitoneal (IP) Vit C, GSH or a Vit C—GSH combination.
- Tumors grew rapidly in all mice despite treatment; the group that had the slowest tumor growth was the Vitamin C only group. After 30 days any surviving mice were euthanized.

- The group with the highest survival percentage at euthanasia was the Vitamin C + GSH group; approximately half the mice were still alive. In the Vitamin C only group, approx. 40% of the mice were still alive.
- The mice that got the IP GSH were given huge doses; 800 mg/kg. Scaled up this approximates to 45–70 g GSH in a human. No rationale is given for such high doses. This is not a clinically relevant dose, neither was it given intravenously as is typical in clinical practice.

In Vitro Studies

One current and often quoted theory about how Vitamin C works in cancer treatment is via the pro-oxidant effect, i.e. Vitamin C is a pro-drug for the formation of hydrogen peroxide. This effect is demonstrated reproducibly in abundant in vitro research, including in the Chen et al. [40] paper. Most current clinical cancer treatment papers using Vitamin C address this theory in the preamble.

A typical statement is that GSH interferes with this, i.e. Vitamin C is working overall as an oxidant and therefore GSH as an antioxidant abolishes this. This is the finding in the Chen et al. paper discussed above.

Vitamin C in its reduced form (ascorbate) can *only* donate an electron. It is a reducing agent, not an oxidant. GSH does the same thing, it is a reducing agent and it donates an electron, just like Vitamin C. Therefore, it would not be surprising to find research that states that GSH has this pro-oxidant effect as well, i.e. that GSH acts as a pro-drug for the formation of hydrogen peroxide. One does not have to look too far for papers that have made this conclusion [63, 193, 235]. For example, [193] state that:

- "The cytotoxic effect of extracellular glutathione, related to membrane metabolism, is mediated by production of H_2O_2 leading to DNA damage and a cellular response involving p53".

Solov'eva and colleagues [235] stated that:

- "The thiols GSH and NAC widely used as antioxidants, in combination with vitamin Bl2b show pro-oxidant characteristics and induce, with the participation of intracellular iron, apoptotic HEp-2 cell death".

There are also papers like this for other antioxidants. Both Vitamin C and GSH act as pro-oxidants in vitro. Both lead to H_2O_2 generation and both kill cancer cells in vitro. The pro-oxidant GSH research reads just like the Vitamin C research—the effect is due to H_2O_2 generation and is abolished by catalase. However, their actual mechanisms of action almost certainly go far beyond the hydrogen peroxide effect.

GSH has not been extensively researched in cancer as a cytotoxic because in vivo it does not appear to do this. Cases and studies of obvious success with GSH therapy as a first line cancer treatment are glaringly missing, despite the above-mentioned pro-oxidant effect. Of importance to note, GSH is not typically given to patients in hundreds of grams doses like Vitamin C. Also, GSH has totally different pharmacokinetics to Vitamin C. Distribution of GSH and Vitamin C following an intravenous dose are different, they do not reach the same concentrations in the same places and essentially do different things in different places in vivo. The high levels of GSH found in some cancer cells are due to cellular production, i.e. the disrupted machinery of the cancer cell genome. This is not related to the physiological levels found distributed elsewhere and is unlikely to be changed by low level exogenous dosing.

GSH is not generally intended as an active cancer treatment, it is used for protection of antioxidant capacity in the patient. Total antioxidant capacity is related to quality of life and some studies say related to survival. Also, GSH in human clinical treatment is massively lower than the doses given to the mice in the Chen et al. study. Lower doses plus systemic distribution suggest that GSH will not reach cancer targets in anything like the concentrations used in the Chen et al. study. GSH is not realistically a first line cytotoxic treatment in the clinical doses currently employed.

N.B. Human clinical trials in cancer do not show negative effects with GSH therapy. Human clinical trials do not show that GSH therapy increases drug resistance.

Do Anti-oxidants Have an Essentially Pro-oxidant Effect In Vivo?

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Many papers demonstrate the pro-oxidant effect of Vitamin C and various other antioxidants in vitro. Only one paper has investigated this for Vitamin C in vivo, Chen and colleagues [39]. They report that:

- "The data show that pharmacologic ascorbate is a prodrug for preferential steady-state formation of Asc(*-) and H_2O_2 in the extracellular space but not blood".
- "Probes to collect ECF eluate were flushed with saline for 30 min and samples were collected over 30 min".

There are two essential problems here. Firstly, before collection of extracellular fluid considerable change has been made to the microenvironment through flushing of the inserted microprobe for 30 min with normal saline PRIOR to obtaining a

sample of the extracellular fluid. The basis for this collection technique is a method published by Tossman in 1986 for the collection of amino acids and not the very labile Vitamin C. Secondly, ECF (extracellular fluid) and blood have to be collected and analysed, collection by definition is ex vivo and exposes the collected fluid to an environment that is different to in vivo conditions. This by its nature changes the redox environment of Vit C and the large risk is that products formed may not be the same ones or at the same concentration as seen in situ in the animal. In vitro and ex vivo Vitamin C research has a long history of drawing conclusions gleaned from experimental artefacts. The paper by Michels and Frei [167] sets some of these out:

- "In human cell culture, the primary issues are the high oxygen environment, presence of redox-active transition metal ions in culture media, and the use of immortalized cell lines grown in the absence of supplemental ascorbic acid. Studies in animal models are also limited due to the presence of endogenous ascorbic acid synthesis".

Also common cell culture media used in in vitro research are probably unsuitable for researching the complex redox interactions of Vitamin C. A recent study by Mojic et al. [174] looking at various controls on the experimental methods used to detect hydrogen peroxide production by Vitamin C has shown us a glaring problem:

- "A drawback in all the in vitro studies was their failure to take into account the in vivo concentration of iron to supplement cell culture media which are characterized by low iron content. Here we showed, using two prostate cancer cell lines (LNCaP and PC-3) and primary astrocytes, that the anticancer/cytotoxic effects of ascorbate are completely abolished by iron at physiological concentrations in cell culture medium and human plasma".
- "These findings show that anticancer effects of ascorbate have been significantly overestimated in previous in vitro studies, and that common cell culture media might be unsuitable for redox research".

Another study by Clement et al. [47] found issues with respect to culture media:

- "In this report, using three different cell types and two different culture media (Dulbecco's modified Eagle's medium and RPMI 1640), we show that the toxicity of ascorbate is due to ascorbate-mediated production of H_2O_2, to an extent that varies with the medium used to culture the cells".

In vitro research should reasonably reflect what is seen in clinical trials and cases. Vitamin C in vitro research demonstrates overwhelmingly a concentration-dependent killing effect on a variety of cancer cell lines. In living patients this is not so simple. These kinds of spectacular results are glaringly absent. Several clinical trials of high dose IV Vitamin C in cancer, with or without chemotherapy have been conducted. While the patients recruited into these trials are obviously very sick, none have been reported to have remission from Vitamin C therapy. In general it would be expected that patients have better quality of life and

better tolerance to their medical therapies with diminished side effects. This is also the case with clinical GSH cancer research.

Killing Effects of Vitamin C in Various Cancer Cell Lines Independent of H_2O_2 in Several Lines of Research

There is significant evidence that Vitamin C blocks KRAS in some colon cancer cell lines, probably also some pancreatic cancer cell lines but unknown at this point. High Vitamin C levels negate GST expression via KRAS and BRAF, not related to H_2O_2 [4, 170, 206, 248, 280]. If you can block KRAS then the cancer doesn't produce as much GST, problem solved or at least improved, independent of exogenous GSH.

Also not related to H_2O_2 are a variety of other studied mechanisms of Vitamin C toxicity in various cancer cell lines, including control of gene demethylation, control of deoxyribonuclease genes, effects on cell cycle arrest and control of intracellular Ca and Fe chemistry.

Whatever the ultimate mechanism of action against cancer cells, in vitro and in vivo, it involves cancer cell death. In vivo there are probably mechanisms, such as generalized immune stimulation, inhibition of angiogenesis, hyaluronidase inhibition, collagen growth (to contain tumors), that are not easily quantified in vitro. Researchers in the Vitamin C and cancer field have succumbed to the temptation to apply the orthodox reductionist singularity approach of hydrogen peroxide production being the only mechanism by which high-dose Vitamin C works against cancer cells—this is most unfortunate, as so much excellent research is not being properly pursued and debated.

Summary

Clinical trials using combinations of Vitamin C and GSH in cancer patients have not been conducted. Only one animal trial has looked at this combination with no clear interpretation of results. In vitro trials with redox reactive reagents like Vitamin C and GSH are notoriously flawed and difficult to control. Typically, information from in vitro or ex vivo trials is not reliable, variations in culture media and experimental handling lead to artefacts that can lead to incorrect conclusions. These trials certainly should not be used to inform clinical approaches unless a relationship is firmly established. To date this is not the case.

There are now many cases where Vitamin C and GSH have been used in combination therapy. These cases are unpublished but ripe for review. Due to the large dose of Vitamin C and small dose of GSH employed in these treatments, it would not be expected that GSH will have any significant impact on cancer cell

toxicity. The main goal essentially is to maintain the antioxidant capacity of the patient so that other more targeted therapies can be used more effectively with lower toxicity, the goal being to maintain the quality of life of the patient and potentially improve survival.

The use of collateral antioxidants in the treatment of cancer has both clinical and scientific support. The Chen et al. [39] experiment needs to be repeated to give more clinically meaningful results: to include physiologically/pharmacologically relevant levels of the intervention drugs and treatment continued until survival or natural death for all animals in the cohorts. Until there is conclusive evidence against the simultaneous use of Glutathione and Vitamin C, it would not seem imprudent to continue such a protocol. It remains to be firmly established what is the best combination of antioxidants and other nutraceuticals (including Vitamin K3, Vitamin D3 and Selenium) for long-term survival and for use with orthodox cytotoxic therapy to increase its efficacy and decrease side effects. If at any stage it is clearly demonstrated that one or two grams of Glutathione and megadose Vitamin C (commonly 15 g up to 100 g) should not be administered at the same time, then naturally practitioners should cease this practice.

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Chapter 8
Bringing It All Together

In this chapter we explore:

- What the patient takes home with them from an integrative medicine consultation
- Some ideas on creating an individualised Wellness Plan
- Why an integrated care model of health works
- What integrative medicine might need to look like in the future.

Introduction

The European Prospective Investigation into Cancer and Nutrition-Potsdam Study which included 23,153 German participants investigated the impact of four factors on the risk of developing several chronic diseases, with a follow-up of 7.8 years:

1. Never smoking
2. Having a BMI <30
3. Performing $\geq$ 3.5 h of physical activity per week and
4. Adhering to healthy dietary principles: high intake of fruits, vegetables and wholegrain bread and low meat consumption

The study found that the risk of developing a chronic disease decreased progressively as the number of healthy factors increased. Compared to participants without one healthy factor, participants with all four factors at baseline had a:

- 36% lower risk of getting cancer
- 93% lower risk of developing diabetes
- 50% lower risk of stroke
- 81% lower risk of myocardial infarction [1].

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What would have made this study more interesting is if they had included additional factors such as stress reduction, sunlight exposure, vitamin D levels and sleep. Nonetheless, this study serves as an illustration that the more a person can address key factors that contribute to poor health and adopt behaviours that contribute to good health, the better their health outcomes are likely to be.

As clinicians, we often meet the patient when something has already gone awry and they are ill. We don't often get to see them when they are healthy and are just having a check-up to make sure they are doing okay. Perhaps that's changing a bit, particularly in the corporate world where companies are now realising the value of their employees having health checks as a preventive measure—as it does no doubt cost companies a lot more when employees do get sick at work. As an aside, at the National Institute of Integrative Medicine in Australia, for example, we run an 'Integrative Health Check' which involves a comprehensive health check-up with an integrative medicine doctor, a naturopath and an osteopath. Some of the investigative technologies used include standard pathology blood tests, heart function analysis using a vascular compliance machine, hair analysis (toxicity and nutritional status testing) and live blood analysis. The person goes home with a folder full of information, including results of their tests and information about health, and a plan about what they can do to improve health.

Back in our consulting room with our patient in front of us, it's our job to assist them to understand what factors may be underpinning their ill health, how to make changes, and why, as well as some of the evidence behind our recommendations. It is about helping them become the Ultimate Patient, one who is empowered with knowledge and who is proactive about making the necessary changes to become as healthy as possible. As we have said on a few occasions now, a healthy patient with cancer will do better than an unhealthy one. Also, even for patients who are at the end of their journey and are in palliative care, there is much that can be done to keep them as comfortable as possible physically, emotionally and spiritually. The key is the patient's will to make the necessary changes to a healthier way of living, to form new healthy habits. Most of us are creatures of habit, so our task as clinicians is to help our patients form healthy ones. It will take discipline on the part of the patient.

In This Chapter

We started this book with the premise that you need the Ultimate Patient to obtain the Ultimate Result. We have devoted Chap. 1 to the features of how to conduct an integrative medicine consultation, and Chaps. 2–7 to the information that can form part of the conversation during the integrative consultation, as well as the evidence behind the various recommendations. In this final chapter, we will focus on the last two features of the Ultimate Consultation:

- *The patient takes home something tangible at the end of the consultation*
- *The Integrated Care Model provides the framework.*

What the Patient Takes Home at the End of the Consultation

There is a lot of information for a patient to try to remember in an integrative medicine consultation. It therefore helps to have some take-home information that can be given to the patient and their support person at the outset and worked through during the consultation. Professor Sali provides his own patient notes, which were the original basis for this book. We find that a lot of patients will come with a notebook to take notes, and this is a good sign, as it shows a level of commitment to learning how they might help themselves.

The written information provided by Professor Sali to his patients follows the Seven Key Health Strategies discussed in Chaps. 2–7:

- Reducing and unloading the storage of life stresses, and harnessing the power of the mind (Chap. 2)
- Eating healthy food (Chap. 3)
- Getting adequate sleep (Chap. 4)
- Getting a daily dose of sunlight (Chap. 5)
- Exercising (Chap. 6)
- Taking supplements and herbal medicines (Chap. 7)
- Exploring innovative investigative technologies and therapies (Chap. 7)

Professor Sali and colleagues have also written a short publication suitable for any patient seeking better health, entitled: *The NIIM Roadmap to Wellness*, which is a preventive healthcare guide providing general advice on three pillars of health-mind (reducing stress), nutrition and movement.

We often recommend books on nutrition that are a relatively easy read and contain valuable information about foods that are useful to add to diet. For example, oncologist Dr David Wilkinson's book *Can Food Be Medicine Against Cancer*, is a favourite of Dr O'Brien's, as it sets out information including scientific evidence clearly and in a style suitable for laypersons, not just clinicians.

Creating a Wellness Plan

Another something a patient can take home with them at the end of their integrative consultation is an individualised Wellness Plan. Whilst it is useful to give the patient information in the form of notes, discussed previously, there is also a need to create a strategy to guide how to move forward. A Wellness Plan can be something as simple as a schedule of appointments with various practitioners and perhaps a list of supplements that might be recommended, or it can be more comprehensive and include recommendations and goals in relation to the seven key health strategies that were covered in Chaps. 2–7. Progress toward achievement of such goals can then be reviewed by the patient and clinician at subsequent consultations. For some

patients, the Wellness Plan helps provide useful structure and a plan to follow, and the achievement of wellness goals can promote a sense of empowerment.

The Wellness Plan can be co-created by the clinician and the patient: by creating it together, the patient is taking an active part in setting their own goals and thereby actively participating in improving their own health. This is about helping them become that Ultimate Patient. The Wellness Plan could be developed at the first consultation, or at least started. However there's a more practical reason why it might be best developed at a follow-up visit—it gives the patient some time to work out what they can and can't afford, as all of these therapies and investigative technologies cost money. It's very important to be sensitive to the person's financial situation, and some may be embarrassed to mention costs and what they can afford. That's why it's useful to be upfront with the patient, and let them know that these various complementary medicine options will cost money, give them an idea of costs, and then suggest that they have a think about what they might like to incorporate in their strategy to improve health.

Some of the recommendations might be able to be filled in at the first visit—for example, recommended foods to include in diet, those to avoid, and some supplements that they could get started on. However, other goals could be left blank for the time being. The patient could fill some of them in at home, after digesting the information given to them at the time of that initial consultation, for example, what they might like to try in order to reduce stress. These could then be discussed at a follow-up consultation.

Key Points

- Advise the patient upfront on the costs of the various investigative technologies and complementary therapies.
- Co-creating a Wellness Plan at a subsequent/follow-up visit allows the patient time to digest information and work out what they can and can't afford.
- Co-creating a Wellness Plan with the patient gives them ownership of the strategy and allows them to play an active part in improving their own health.

Key Benefits of a Wellness Plan

There are some key benefits of a Wellness Plan. It can be used to:

- Schedule appointments
- Set wellness goals
- Review progress against goals (self and clinician-review)

Scheduling of appointments

When it is likely that patients will be seeing several doctors and allied health practitioners who are working in a team to assist a patient with cancer, keeping track of appointments can be difficult for patients. For example, a patient may have an initial consultation with the oncologist and integrative medical practitioner, then have appointments with a nutritionalist and exercise physiologist, plus appointments for high-dose Vitamin C therapy and hyperthermia. You can get the idea. Once you have a few practitioners in the mix, a Wellness Plan can assist the patient in keeping track of their various appointments.

Setting wellness goals

A Wellness Plan can also be used to set wellness goals—for example an exercise physiologist may set particular exercise goals, and the patient may use the plan to document their own progress. A nutritionalist might ask a patient to complete a five-day diet diary initially, then suggest modifications to their diet which could be incorporated into the Wellness Plan. The clinician may suggest some sleep hygiene measures—again, these may be included in the Wellness Plan.

Reviewing wellness goals

The patient may use these goals as a way of reviewing their progress or commitment to the goals. The clinician may review progress towards these goals at subsequent appointments, and use the feedback to suggest modifications to the plan and/or offer encouragement.

Key Points
A Wellness Plan can be used to:

- Schedule appointments
- Set wellness goals
- Review progress against goals (self and clinician-review)

Suggestions for a Framework for the Wellness Plan

To create a Wellness Plan for your clinic, you need to decide firstly if the purpose is simply to provide a schedule of appointments or whether you want it to be more comprehensive, for example covering the seven key health strategies that we have included in this book. The Wellness Plan could simply provide an introduction, then topic headings with spaces left blank to be filled in during or after the consultation, then a list of contacts.

Some suggestions of what could be included are set out in Table 8.1.

Table 8.1 Suggestions of what to include in a wellness plan

Welcome and introduction to the clinic	This could be a one-pager that welcomes the patient to the clinic, provides an explanation of the philosophy of the clinic and the modalities offered, a brief introduction to the clinicians, and contact details of the clinic including Emergency Contact phone numbers
Stress reduction	This could include space to write down different strategies to reduce stress. Where meditation classes are recommended, the contact details of a meditation teacher might be included, for example
Diet	This might include space to list foods to incorporate into diet and foods to avoid
Sleep	Where sleep has been identified as an issue, this section could include some suggested sleep hygiene goals and details of some sleep enhancing therapies that could assist e.g. acupuncture, homoeopathy. Where supplements that might assist are recommended, these could be listed here
Vitamin D and sunshine	This section might list some goals for getting adequate sunshine, and an appointment schedule for assessment of vitamin D levels (if this has not been done) and re-assessment. Where Vit D supplements are recommended, this section should include recommended dosage and date for re-assessment to monitor vitamin D levels. Where IV vitamin D is recommended, the Wellness Plan should also include a re-assessment date
Exercise	If the clinician is skilled in exercise therapy, then this section could list some types of exercise that can be incorporated into the patient's lifestyle. However, since many patients have co-morbidities that might preclude some of the simple exercise suggestions such as moderate walking or yoga, for example in a cancer patient with arthritis, an exercise plan is best handled by an exercise physiologist. Such professionals are trained to consider the various factors that need to be taken into consideration
Additional therapies This section could be subdivided into several sections, for example: • High-dose IV vitamins • Oral vitamin supplements • Complementary medicines and therapies • Innovative technologies and therapies	
High-dose IV vitamins	This section of the Wellness Plan should include a schedule of appointments, taking into account when the patient might be having other therapies. For example, in an integrative clinic in Hong Kong,

(continued)

Table 8.1 (continued)

	patients who are having IV Vitamin C therapy also have acupuncture whilst they are sitting with the IV drip in their arm. In the National Institute of Integrative Medicine (NIIM) clinic in Australia, patients having hyperthermia may also have high dose IV Vitamin therapy delivered at the same time
Oral vitamin supplements	This section will include those recommended supplements including dosages
Complementary medicines and therapies	This section might simply include the contact details of the allied health/complementary medicine practitioner(s) (e.g. Chinese herbal medicine practitioner, acupuncturist, Western herbalist, homoeopathy practitioner, massage therapist) who are recommended by the integrative medicine doctor. The complementary medicine practitioner can then discuss the schedule of appointments with the patient, which could be inserted into the Wellness Plan as an attachment
Innovative technologies and treatments	Where an integrative medicine clinic provides additional, innovative diagnostic techniques e.g. circulating tumor cell testing and therapies such as hyperthermia, this section could include a schedule of appointments in relation to these

Working in an Integrated Healthcare Team: The Integrated Care Model of Practice

It's very difficult to be an expert in everything, even for an integrative medicine doctor. An integrated care model is one in which a team approach to patient care is taken, one involving several practitioners of allied health and complementary medicine who work together with the general integrative medical practitioner and oncologist. An integrated care model is not one doctor trained in western medicine who is also trained in some additional form(s) of complementary medicine trying to manage the patient on their own.

Most patients with cancer have an oncologist and they also have a regular general practitioner or family doctor who plays an important role alongside the oncologist. If this general practitioner is an integrative medicine doctor, so much the better but it's certainly not essential for the integrated care model. What is important is an open-mind and respect for other health professions. Other members of an integrated healthcare team include: nursing staff, nutritionalists, naturopaths, Chinese medicine practitioners, exercise physiologists, psychologists, meditation teachers, massage therapists and others.

Whilst some integrative medicine doctors have trained in additional complementary modalities, in particular nutrition/nutritional supplements, it is a rare one

that knows the lot and is skilled in several forms of complementary medicine. It really does make sense to co-manage in a team and utilise the expertise of colleagues. The integrative medicine doctor or oncologist is in the ideal position to be the central pivot of the patient's care.

Team Meetings

The ideal model is for a team to meet face-to-fact to discuss the patient's case and agree on what different modalities may best help the patient. Then a range of options can be discussed with the patient who can make decisions about what they want to do, taking into consideration affordability, distance to travel and other practical considerations. In the end, it's the patient's decision—they may gravitate towards some therapies more than others, and that's okay.

In practice it is sometimes difficult to get practitioners together, in particular if they don't work in a multidisciplinary practice. However, you can work around this by using phone conferencing at a designated time. At this meeting, each person can discuss what their modality can contribute, and how frequently they might need to see the patient (for example, a nutritional medicine practitioner may want to see a patient every 3–4 weeks to monitor how they are doing with supplements and diet modifications, whereas an acupuncturist might want to see the patient on a weekly basis). The integrative doctor is ideally placed to coordinate and can monitor the patient's progress.

Orthodox therapy may take precedence at certain times because of the time intensiveness of therapies such as radiation therapy. This needs to be considered in planning their care.

If your practice is very organised and it is possible, having a designated Patient Liaison Officer for each cancer patient is ideal. The Patient Liaison Officer can be the first point of contact for questions in relation to the Wellness Plan, various therapies, appointments and other topics, and where necessary, the Patient Liaison Officer can refer medical questions quickly as appropriate.

If it is not possible to bring a team together at the one time, then ideally the integrative medicine doctor will have a referral network of allied health/complementary medicine practitioners that they can refer the patient to, and who can provide regular reports to the doctor. The Wellness Plan would therefore include the contact details of those allied health/complementary medicine practitioners whom the doctor may recommend.

At the end of the day, there is much that complementary medicine can offer patients in conjunction with orthodox medicine.

Expanding Integrative Medicine

Integrative Medicine will be the medicine of the future. The public are already practising integrative medicine—they are seeking their own answers to health and healing through a variety of means. We already know that a substantial percentage of Australians, Americans and those living in other Western countries are using complementary medicines, with or without the knowledge of their general practitioner.

In other parts of the world, forms of 'natural medicines' such as herbal medicine, acupuncture and others, are not 'alternatives'. In their countries of origin, such medicines are the original medicines. In fact, when western medicine was introduced to many countries, such as China and India, each of which had their own medical systems, western medicine was at one point the 'alternative medicine'. The use of such labels such as 'alternative' and 'complementary' is a western one and an epistemological claim, one that asserts the pre-eminence of western medicine over other forms of medicine.

Like many of the problems in this world, the problem of illness will not be solved by competitiveness and warring factions within and outside of medical communities, however you define medicine. It will be solved by the spirit of cooperation, open-mindedness and mutual respect between the many different groups involved in healthcare and the communities that they serve. It will require political leaders with a deep understanding of public health—real public health—who are willing to make the changes necessary to enable the practise of integrative medicine, because that is what the public are practising and clearly wanting. This may require a fundamental change in health funding models, away from one that enables quick medical consultations with too often limited health outcomes, to one that facilitates an integrated care model that includes evidence-based complementary medicines along with evidence-based orthodox medicine—real integrative medicine. The ultimate aim is to deliver the best possible care to the patient.

Education

Medical education, and education more broadly, will need to shift gears. At the level of primary and secondary schooling, at least in Australia, we are not doing enough to teach our children how to cope with stress, nor the effects of stress on mental, emotional and physical health. Children need to learn how to communicate about stresses and how to unload.

We are not recognising in our work practices how much we are damaging ourselves through a lack of work–life balance. We are not educating our young people, at school where much of this education (but not only there) should take place about the pressures of the workplace, the insidious culture to conform to

overwork, and how to create balance. Instead we promulgate a culture of overwork and wear it like some badge of honour. It's a very stupid and dangerous practice.

Clinicians have an important role to play in educating their patients and often, the families of those patients consequently. However, education must start much earlier than that, in primary and secondary schools and colleges.

In the clinic, as clinicians we need to be paying far more attention to talking to our patients about stress, and how they can unload stored stress and emotions. There is plenty of 'scientific' evidence of its role in pathogenesis of chronic diseases such as cancer. We need to help our patients understand what their stresses are, and how to reduce them or 'unload' them. To do this, we need time to talk with our patients and listen.

Environment

According to Professor Sali, the single most defining word that describes the behaviour of humans throughout history is 'killing'. Fortunately, since the loss of over 50 million people in the Second World War, in the Western world at least killing has become far less popular. But we are doing other things to kill ourselves, albeit more slowly. We are poisoning our waters and our food supply and our air, and we are wondering why the proportion of people with cancer and other chronic illnesses are so high. We are running around throwing money at research to find cures for the very diseases that we, as a species, are creating. It's not rocket science. We are confusing the issue of poisoning our environment when we talk about things like carbon trading schemes, as these are meaningless to most people, and they are not addressing the root causes of environmental damage, which is our behaviour.

Redefining Integrative Medicine

At the beginning of this book, we described Integrative Medicine as follows:

Integrative Medicine combines conventional medicine with evidence-based complementary medicines, therapies and lifestyle interventions for the treatment and prevention of disease. The patient–practitioner relationship is collaborative and supportive, empowering patients to take control of their health and wellbeing. Integrative medical practice makes use of all appropriate therapeutic approaches, healthcare providers and disciplines to achieve the best health outcome for each individual patient. Integrative Medicine empowers patients and health practitioners with a wider range of treatment, screening and prevention options, a collaborative relationship, and an emphasis on preventative medicine. It is a form of medicine through which the clinician can deliver health to the public; in a sense it enables public health.

This definition has a heavy emphasis on what has caused disease at the individual or personal level, in contrast with orthodox medicine. It's not a bad definition, at first glance. However, Integrative Medicine will need to include more than this. Health cannot occur in isolation to our environment and the way we live. To be truly integrative in medicine, we need to go back to the wisdom of many ancient cultures which understood the human as existing as one part of the environment, affected by and capable of affecting the world around it. Our health is intimately interwoven with our food supplies, our industries, and our ways of living and interacting with others. Our health is also interwoven with our spirituality, which is something beyond religion, and something we have chosen not to address in this book. Nonetheless, this is a very important part of health.

Those are only a few factors that impact on our health. If we want to see changes in population health, we need to make changes to how we approach living on this earth. The ancient cultures including the North American Indians understood this. They are warning us again right now about the potential devastation of rivers and waterways in the US.

Integrative medicine in the future must involve more than practitioners of medicines, whatever the form these 'medicines' may take. We need to come back, like a council of elders, to reconsider the many factors inherent in how we live our lives as societies or nations that are adversely impacting on our environment and consequently, ultimately on our health, and we need to make changes to these. Discussions about public health will need to involve various industries, environmental experts, town planners, educators and many other sectors of society, because the actions and behaviours of these many sectors all impact on health. We need to learn to cooperate as a species, or we face extinction. We also might need to better define 'health'.

Black Elk said:

> I could see that the Wasichus [white people] did not care for each other the way our people did before the national's hoop was broken. They would take everything from each other if they could, and so there were some who had more of everything than they could use, while crowds of people had nothing at all and maybe were starving. 'They had forgotten that the earth was their mother'. (John G Neihardt, Black Elk Speaks: The Complete Edition)

Conclusion

This book has sought to capture an approach to conducting an integrative consultation, with a focus on patients with cancer. Whilst we have chosen cancer for the purposes of this book, the principles described in this book equally apply to other chronic diseases. The impact of stress, nutrition, sleep, vitamin D, exercise and additional therapies could easily apply to cardiovascular disease, or rheumatology, for example.

Such an approach to conducting an integrative oncology consultation does not reduce the person to a diagnosis. It seeks to see the human being as they are, a person living with cancer. This book has sought to give some guidance to clinicians working with cancer patients about the many factors that can contribute to cancer, some health strategies that can contribute to wellness and some of the scientific evidence associated. It is based on Professor Avni Sali's approach to working with patients with cancer and other serious diseases.

There is a massive amount of data on integrative medicine and its application to cancer. We have made reference to some of this, and have we presented some of the key evidence in relation to what we have discussed. We have not covered all complementary medicines and innovative therapies that may show promise in the treatment of cancer. Instead, we chose to focus on particular ones and present some of the scientific evidence in relation to those.

One of the underpinning premises of the Ultimate Consultation is that the Ultimate Outcome requires the Ultimate Patient, one who is empowered and proactive in making positive changes to adopt a healthier lifestyle. Another key premise is that a healthy person with cancer will do better than an unhealthy one. Stress is one of the most important factors in illness and healing from conditions such as cancer will require identifying and alleviating stress, through the unloading of stored emotions and stress. Better still if we can prevent cancer in the first place by addressing life stresses. Happiness is very important to nurture.

It is hoped that this book may give those interested in working with people with cancer some ideas of how they might construct their own approach to an integrative oncology consultation, and some of the evidence behind many of the integrative medicine approaches that may be used. Importantly it is hoped that it may help clinicians help empower their patients to harness the power of their minds to make necessary changes and provide the necessary fire to maintain the discipline needed to form new and healthier habits. This notion of harnessing of the mind is not just wishful thinking. We have enough 'scientific evidence' to now understand the physiology behind it. We just don't really know what the mind is…

Finally, we would like to end this book with a story about a well-respected Australian athlete who faced his own challenges with health, and in many ways, exemplifies the power of human will and the necessity of discipline in turning a difficult situation around.

Nothing New Under the Sun? A Tale of an Australian Athlete

There are numerous stories of individuals who have reversed severe health problems by changing lifestyle, diet and physical fitness. Kylie's father recounts one such story from his adolescence in Shepparton, Victoria in the middle of last century and this story illustrates in many ways what can be achieved with intention, willpower, and importantly discipline.

Her father spoke of meeting a man named Percy Cerutty who, approaching 50, had a life-threatening health breakdown. He refused to die, adopted a strict vegetarian diet, and took up long distance running. Percy began training to tackle an Australian 50-mile record, the attempt which was to finish at a big sports gymkhana being staged by Kylie's grandfather Bill O'Brien, a well-known boxing trainer who trained several Australian boxing champions. Her father, Les O'Brien, describes the experience thus:

> He stayed at a local pub, but had many of his lunches with us. My mother would simply cut up the largest variety of fresh, raw vegetables and fruit that she could muster on his plate. He would begin running from the pub, in his sparse uniform of short shorts and running shoes (there's your vitamin D!), eat his meal, then head off to knock up as many training miles as the afternoon would allow. He was an excellent conversationalist, and indulged my adolescent curiosity about his change in lifestyle and ambitions. Did he break the record? I've forgotten. But he did write me a letter later, which I kept for many years, in which he explained what he called the philosophy of his new lifestyle, which he called 'Stotanism', a cross between Roman stoicism and Spartan self-discipline. Instead of an early demise, from those early years, 'Stotan' Percy embarked on a long career as an athlete's training coach, mentoring such famous Olympic runners as Herb Elliot and Betty Cuthbert and countless others, and not just runners, at his training camp in Portsea, on the coast, where he ran his trainees up and down sand hills and preached his philosophy of healthy living.
>
> There are numerous books written about Percy Cerutty, including one of his own entitled 'Why Die?'. Percy certainly would have to be Professor Sali's ultimate 'Ultimate Patient'.

Quod Erat Demonstradum
(*That which was to be demonstrated*)

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